Neurology

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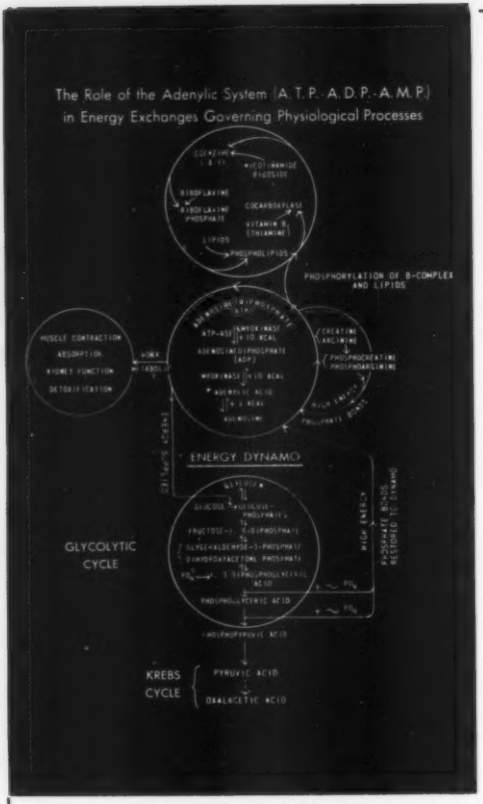

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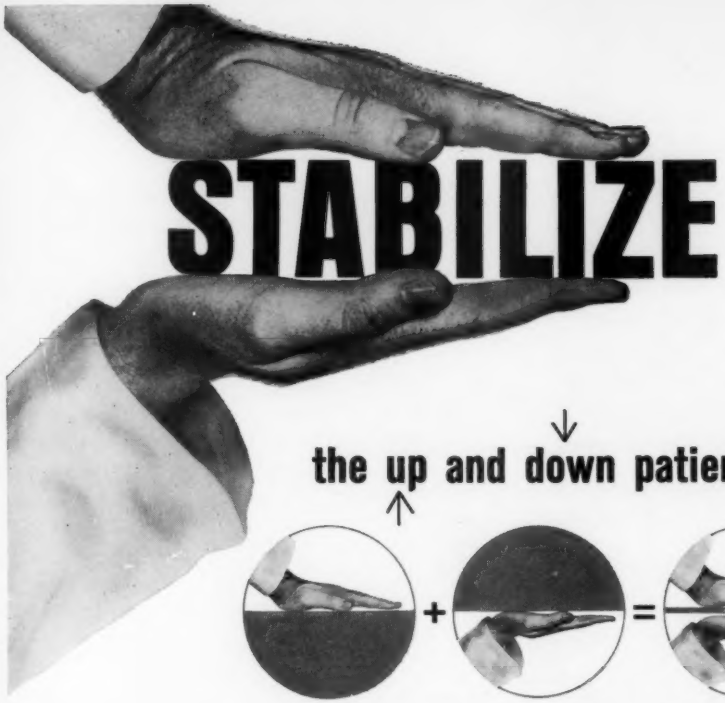

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1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M. C.: Personal communication.

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1. Braceland, F.J.: Texas State J. Med. 51:287 (June) 1955.
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1. Livingston, S., and Petersen, D.: New England J. Med. *254*:327 (Feb. 16) 1956.
2. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.
3. Berman, B. A.: Am. J. Psychiat. *112*:541 (Jan.) 1956.

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NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

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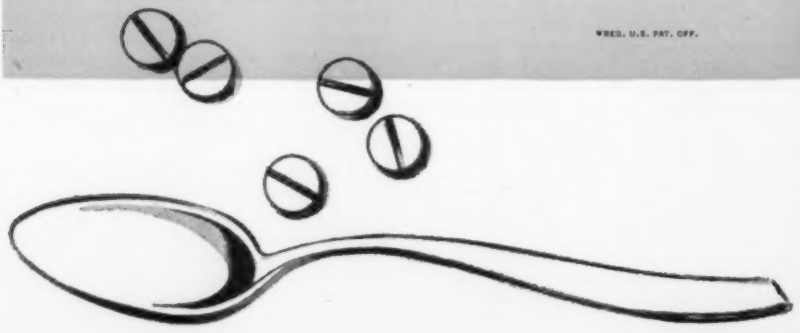

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1. Hollister, L. E., Krieger, G. E., Kringel, A., and Roberts, R. H.: Ann. New York Acad. Sc. *61*:92 (April 15) 1955. 2. Hoffman, J. L., and Konchegul, L.: Ann. New York Acad. Sc. *61*:144 (April 15) 1955. 3. Kline, N. S., and Stanley, A. M.: Ann. New York Acad. Sc. *61*:85 (April 15) 1955.

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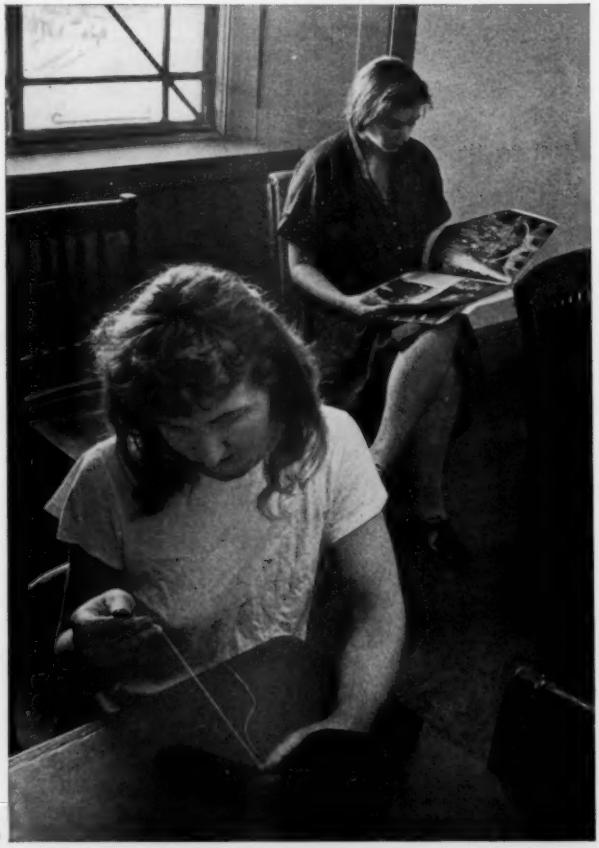

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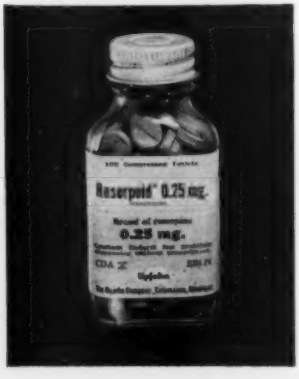

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Volume 6 Neurology *Number 10*

Otitic Hydrocephalus

Sir Charles Symonds

OTITIC HYDROCEPHALUS is a term which I myself devised 25 years ago, and, as has often been pointed out to me, it was a misnomer. This was in part appreciated when the author wrote a second paper on this subject in 1937,[1] but it was Gardner[2] who first demonstrated by air studies the absence of ventricular dilatation in this syndrome and suggested that the term "otitic hydrocephalus" should be abandoned in favor of the descriptive title "sinus thrombosis causing intracranial hypertension." However, the clinical picture in the otitic cases differs from that of sinus thrombosis arising from most other causes, which is doubtless why otitic hydrocephalus is still used to describe this syndrome. Bradshaw[3] recently summarized it thus: "It is," he said, "generally the story of a child who has had a recent aural infection, develops a squint owing to a paralysis of one or both external recti and complains of headache. This leads to examination of the optic fundi and the discovery of papilledema . . . In many cases," he added, "headache is entirely absent." To complete the picture, let us add that in some instances the otitis has been chronic rather than acute, that in a significant proportion of the cases there has been evidence of lateral sinus thrombosis, that the patient is alert and active, despite the papilledema, and that the cerebrospinal fluid, though under increased pressure, usually shows no increase of cells or protein. Bradshaw stressed the sixth nerve palsy, and indeed it was present in 19 of the 21 cases he presented from the records of the Radcliffe Infirmary at Oxford, where Cairns' clinical acumen led to the early recognition of the syndrome. In the 11 cases recently reported by Foley,[4] a sixth nerve palsy was present in eight, though in 46 cases collected from the

Read at the eighth annual meeting of the American Academy of Neurology, St. Louis, April 28, 1956.

87, Harley Street, W.1, London, England.

literature he found it recorded in only 14. It is quite likely that the complaint of blurred vision in a child with intense papilledema was not always investigated with sufficient care. It has been the author's experience that diplopia in some degree is usually found in these cases as the result of external rectus weakness.

Anyone who begins to speculate about the pathogenesis of this syndrome must at once be impressed by the frequency of lateral sinus thrombosis. Among the cases collected from the literature by Foley,[4] thrombosis of a lateral sinus or granulations on its wall were observed at operation in 25 out of the 46 cases. In his own series of 11 cases, involvement of the lateral sinus was found in two of the four in which the sinus was inspected. In Bradshaw's series the incidence was lower, two out of nine exposed lateral sinuses being thrombosed. Postmortem evidence is fortunately rare, for the syndrome is benign, but all the more valuable when obtained. Foley has summarized six fatal cases from the literature, among which he included one reported by Carmack[5] in which no sinus thrombosis was found at autopsy, but reference to the source shows first that the case presented none of the clinical features of otitic hydrocephalus. The patient, aged six, was admitted to the hospital with bronchopneumonia and fever ranging from 103° to 105° F. Otitis media was an incidental finding. There was no papilledema and the cerebrospinal fluid pressure was no higher than 150 mm. Second, there was no record in the autopsy notes that the dural sinuses were examined. In the case published by Davidoff and Dyke[6] there is no record of any examination of the dural sinuses. This leaves us, therefore, with four cases of the group reviewed by Foley in which clinicopathologic correlation was reasonably complete, and in each of these dural sinus thrombosis was found. To these must be added another record of particular importance because the patient was recovering from otitic hydrocephalus when he died from endocarditis. This was the case published by Bailey and Hass[7] in 1937, and here also dural sinus thrombosis was proved.

There can be no doubt from this evidence that dural sinus thrombosis is the cause of otitic hydrocephalus, but the mechanism of the increased intracranial pressure remains to be explained. Here Gardner[2] has proved right in his concept of venous engorgement with consequent cerebral edema. It has been the experience of all observers that in these cases the ventricles are of normal size when filled with air, or rather smaller than the average, and this can only be associated with increased intracranial pressure if the brain itself is swollen. An earlier suggestion that mural thrombosis in the superior longitudinal sinus might be the cause of otitic hydrocephalus from obstruction of the arachnoid villi blocking the outflow of cerebrospinal fluid was made before air studies had thrown light upon the subject.

We have still, however, to investigate how far dural sinus thrombosis must extend from the lateral sinus to produce this clinical picture and what other factors may be causal. Can occlusion of one lateral sinus in itself cause otitic hydrocephalus? Against this is the observation that the syndrome develops in only a very small fraction of cases in which sinus thrombosis has been proved at operation. Moreover, on theoretical grounds we should not expect the oc-

clusion of one lateral sinus to cause any considerable or lasting obstruction to the venous outflow from the cranium, provided that the anastomosis at the torcular follows the conventional pattern. Woodhall[8] has shown that one or other lateral sinus is absent in something like 4 per cent of people, both the superior longitudinal sinus and the straight sinus draining into the single channel which exists. Its occlusion might well cause enough venous engorgement and consequent cerebral edema to produce the syndrome we are considering. When both lateral sinuses are present, the extension of thrombus from the point of origin up to the torcular would have the same mechanical effect. Having regard to these speculations, the postmortem evidence deserves more detailed study. In Gardner's[2] case 2 the syndrome appeared on the twenty-first day after an acute right otitis media, with papilledema of 4 diopters. Death from meningitis occurred on the fifty-sixth day. Thrombosis was found in the right lateral sinus, extending across to the left lateral sinus into the straight sinus and upward into the superior longitudinal sinus to occlude its posterior two-thirds.

In the case of Bailey and Hass[7] there was thrombosis of the lateral sinus on the side of the affected ear extending upward to the torcular and thence involving the posterior two-thirds of the superior longitudinal sinus. In the author's case[9] in which death occurred suddenly following lumbar puncture three weeks after the onset of an acute right otitis media, the clinical signs were characteristic of otitic hydrocephalus. The pathologist reported, "The left lateral sinus was normal and was the smaller of the two. The superior longitudinal sinus was opened in its whole length and no gross changes found. On following this down to its posterior end, the clot in the right lateral sinus became visible before the straight sinus or the left lateral sinus were opened, so that it appeared that the clotting in the right lateral sinus was obstructing both lateral sinuses."

There remain Gardner's case 1[2] and Ford's[10] case. The postmortem report in the latter, in which death was due to septicemia, states that there was thrombosis of the right lateral sinus, while the other dural sinuses were patent. There is no description of the torcular pattern or the relative size of the lateral sinuses. Gardner's case 1 appears to have presented a typical picture of otitic hydrocephalus with eventual recovery, but two years later the patient had a recurrence of the left otitis media and died of meningitis. At post mortem "the left lateral sinus was represented by a fibrous cord, apparently indicating that thrombosis of this sinus had occurred with the attack of otitis two years previously." Associated with the meningitis was acute thrombophlebitis of the left superior petrosal and superior longitudinal sinuses. There is no mention of the torcular pattern or of the size of the right lateral sinus. It would appear from these two last cases that thrombosis of one lateral sinus alone can cause otitic hydrocephalus, but we are uncertain whether there may have been a contributory anatomic factor. In the other three cases the venous outflow from the level of the torcular was obstructed in all. Further postmortem studies are needed to determine whether and, if so, in what circumstances localized unilateral lateral sinus thrombosis causes this syndrome.

The frequency with which the sixth nerves are involved makes it highly im-

probable that this is simply an effect of increased intracranial pressure. It has appeared to the author[9] more likely that this is due to thrombosis of the inferior petrosal sinus, with compression of the sixth nerve by the clot. This might occur either by extension from the lateral sinus or by direct spread from the middle ear. This mechanism might also afford a better explanation for Gradenigo's syndrome than petrositis, for the sixth nerve palsy may appear in the course of acute otitis media without any evidence of bone infection.

Paralysis of the ninth, tenth, and eleventh cranial nerves, well known as an occasional complication of lateral sinus thrombosis, is also, the author suggests, an example of pressure palsy from clot in the jugular bulb or posterior end of the inferior petrosal sinus. Much more rarely involvement of the fifth nerve is associated with otitis media, the symptoms being pain or numbness in the trigeminal distribution with an impaired corneal reflex. This may be due to thrombosis of the superior petrosal sinus, also with a pressure effect. This has been observed also in two patients with cavernous sinus thrombosis who recovered. The sixth nerve, of course, was already involved, and the affection of the fifth was shortly followed in each instance by paralysis of the ninth, tenth, and eleventh nerves. This sequence was interpreted as the effect of backward spread of thrombosis to the superior and inferior petrosal sinuses. Recovery from these cranial nerve palsies was rapid and complete.

One of the striking features of otitic hydrocephalus is the rarity of any symptoms or signs of cerebral damage. This in itself, as Foley[4] has observed, is reason for supposing that the superior longitudinal sinus is not thrombosed to any great extent, for when this occurs epileptic seizures and hemiparesis are common. The puerperal cases have taught us this. Clot within the superior longitudinal sinus is apt to extend into tributary veins causing local edema and hemorrhage. That this is not an invariable occurrence is proved by the case of Bailey and Hass,[7] in which there was no clinical evidence of cerebral damage and at post mortem only one small area of softening. In this case, in addition to the posterior two-thirds of the superior longitudinal sinus, the torcular and right lateral sinuses were involved, though it is interesting to note that at no point could complete occlusion of any of the sinuses be demonstrated. Whether thrombosis of the superior longitudinal sinus alone may produce the clinical picture of intracranial hypertension without epilepsy or focal signs we do not know. There is no evidence to show that it can.

Focal seizures and hemiparesis may be observed in association with otitis media as an independent occurrence, and in this group of cases too there is a significant number in which lateral sinus thrombosis has been observed. In these patients signs of increased intracranial pressure are the exception rather than the rule. Papilledema was present in none of the six cases belonging to this group reported by the author in 1937,[1] cases in which no abscess was discovered and spontaneous recovery ensued, and it has not been observed in any of the cases seen since then. In a comparable group of 16 cases recorded by Courville and Nielsen,[11] ophthalmoscopic examination was not reported in five. In the remaining cases papilledema was absent in eight and present in three. It would seem that thrombophlebitis of

the superficial cerebral veins is the cause of the focal seizures or hemiparesis, but as a rule there does not exist thrombosis of the dural sinuses of such extent as to cause cerebral edema. The explanation suggested by Courville and Nielsen[11] of extension of thrombophlebitis to the cortical veins, either directly by way of the veins draining from the middle ear into the petrosal sinuses or from the lateral sinus by way of the inferior anastomotic vein, is probably correct.

The diagnosis of otitic hydrocephalus on clinical grounds alone is reasonably certain in many cases without the need of air studies. If these are to be done, it should be by ventriculography because of the danger of a pressure cone. But ventriculography is not always an innocuous procedure. It may often be dispensed with provided that symptoms and signs are non-progressive.

As to the treatment of these cases, it is remarkable how well they do if left to nature. Canalization of the clot and opening up of anastomotic channels are doubtless both operative. The only fear one need have is that of visual failure from secondary optic atrophy. This fortunately is a rare occurrence, but it can happen as in two children observed before the syndrome had been recognized for what it was and before the pneumoencephalogram had been invented by Dandy. After negative explorations for cerebellar abscess both cases became virtually blind. The cautious reduction of pressure by lumbar puncture repeated every three or four days until the manometric reading is found to be 200 mm. or less has appeared to avert the threat to vision, but it should certainly be done cautiously. The pressure should not be allowed to fall below 150 mm. In one case already mentioned,[9] the withdrawal of an unknown quantity of fluid before the patient's admission to hospital was followed within a few hours after admission by another lumbar puncture, when again an unknown quantity of fluid was withdrawn by a house surgeon; a few hours later the patient died suddenly. If the pressure remains above 300 mm. after two or three lumbar punctures and there is any deterioration of visual acuity, subtemporal decompression is probably the treatment of choice.

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Surgical Treatment of Angiographically Localized Intracranial Aneurysms

A Follow-up Report

Carl J. Graf, M.D.

RECENTLY we reported a mortality of 45 per cent in a series of 55 patients with intracranial aneurysms operated upon by the direct approach.[1] This figure, unusually high when compared with other similar series, was derived from a group of consecutively treated patients whose aneurysms were demonstrated preoperatively by angiography in only 62 per cent. In the remaining 38 per cent, aneurysms were found at operation or at necropsy following exploration. These operations were performed at a time when angiography was not as widely employed as at present. In this latter group, although the aneurysms had been suspected preoperatively, they were not specifically localized and therefore operations were not definitely planned. We believe that the exposure of a hidden unpredictable aneurysm, early inexperience in the surgery of these lesions, less efficient technical aids than are now employed, and early operation following subarachnoid hemorrhage materially affected the ultimate mortality rate.

Sixteen of this group of 55 patients had intracerebral hematomas, and 14 of these patients died. Of 20 patients operated upon within two weeks following the initial hemorrhage, 14 expired. In these 14 patients, aneurysms were located on the supraclinoid carotid in three, the anterior cerebral artery in two, the anterior communicating artery in six, and the midcerebral artery in three. Eleven of these patients had intracerebral hematomas. There were one hematoma in the supraclinoid group, two in the anterior cerebral, five in the anterior communicating group of six patients who expired, and three in the middle cerebral group of aneurysms. Three middle cerebral and one anterior communicating artery aneurysms were associated with intracerebral hematomas. Only the hematomas were evacuated; the aneurysms were left untreated.

From these figures it is difficult to tell whether time of operation or the presence of intracerebral hematoma was more important in the fatality rate. In eight of the 55 patients, the aneurysm was not actually attacked. Two of these eight patients had multiple aneurysms, one with an associated intracerebral hematoma which was evacuated only, the

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aneurysms being left untreated. Two calcific aneurysms of the vertebral artery were found. One patient had only one vertebral trunk. Six of these eight patients died; those with the vertebral artery lesions are still alive. If these eight untreated patients are excluded from the series, the over-all mortality rate is 40 per cent.

Since the initial report, we have used the direct approach without fatality two or more weeks following the initial hemorrhage in ten more patients with aneurysms. The mortality rate in the entire group of 65 patients is 38.4 per cent. Excluding the untreated eight patients, the rate is 33.3 per cent. This figure, however, may not be entirely justified because hematomas were removed in six patients, who were treated in part. The mortality in the group of eight patients where the aneurysm was actually not treated was 75 per cent, since six patients died. Fifty-three (81 per cent) of the 65 patients had had previous subarachnoid hemorrhage.

ANATOMIC LOCATION

Aneurysms in this series were located at six sites: six were on the infraclinoid portion of the carotid artery, 28 on the supraclinoid carotid, six on the middle cerebral, eight on the anterior cerebral, 11 on the anterior communicating, and two on the vertebral arteries. Four aneurysms were at the intracranial carotid bifurcation.

TECHNIC OF OPERATION

Where intracerebral hematomas existed, they were removed transcortically. Chemical hypotensive technic with Arfonad or hexamethonium was employed in 14 cases only. We have had no experience with hypothermia in treating intracranial aneurysms. The technic employed in the treatment of the various lesions was as follows:

Infraclinoid carotid aneurysm. There were six patients with infraclinoid carotid aneurysms. Four of these were treated by intracranial clipping of the carotid artery and extracranial carotid ligation. One patient had extracranial carotid ligation and the aneurysm was packed with muscle. In the other, exploration revealed bilateral aneurysms. These were left untreated. The latter two patients (33 per cent) in this group died.

Supraclinoid carotid aneurysm. Thirty-two patients in this series had supraclinoid carotid aneurysms, with four situated at the carotid bifurcation. Seven were successfully treated by trapping the lesion between an intracranial clip and extracranial carotid ligation. One aneurysm was reinforced by wrapping with cottonoid. Two were trapped between clips applied to the carotid on either side of the aneurysm. Two were trapped by intracranial carotid clips alone; one aneurysm was removed, one wrapped with cotton, and another wrapped with muscle after trapping. These patients all recovered.

The aneurysmal neck was clipped in 13 patients, supplemented by reinforcement with cotton in one, and by muscle in another. One aneurysm was trapped intracranially and a clip applied across its neck. Three (23 per cent) of these patients died.

Carotid bifurcation aneurysm. One carotid bifurcation aneurysm had a ligature applied about its neck; one was clipped and reinforced with muscle. In a third patient, the operator's retractor was struck by an assistant while the ligature was being applied, rupturing the

aneurysm. Hemorrhage was controlled with a muscle pack. During dural closure fully one-half hour later, hemorrhage recurred. The carotid and the posterior communicating arteries were clipped. This patient had a postoperative left hemiplegia which has persisted.

The fourth patient's aneurysm ruptured during exposure. This too rebled after muscle packing while the dura was being closed. Secondary clipping after removal of the pack controlled the hemorrhage. This patient died. Necropsy revealed clips on the perforating arteries to the thalamus. The carotid and middle cerebral trunks were free of clot. Muscle packing an aneurysm which has ruptured upon exposure has impressed us as makeshift and inadequate, employed only for want of anything else to do. The mortality in the bifurcation lesions was 25 per cent; one of four patients died.

Two patients with hematomas and aneurysm in the supraclinoid group expired. One patient had multiple aneurysms. An associated hematoma was removed; the aneurysms were left untreated. The total mortality of patients with aneurysms in this location was 15.6 per cent.

Middle cerebral aneurysm. Five of six patients with middle cerebral aneurysms had associated intracerebral hematomas. In three, only the hematoma was removed; these three patients died. In one patient the aneurysm was clipped after clot evacuation; this patient also died. Of the remaining two patients, one had a hematoma removed following clipping and reinforcement of the aneurysm. The other had the lesion reinforced only. Both of these patients recovered. Four of six patients in this category expired, a mortality rate of 66 per cent.

Anterior cerebral aneurysm. In this series there were eight anterior cerebral aneurysms. Three were associated with intracerebral hematoma. The patients with this combination died. In these three cases, the aneurysm was trapped in one, the neck clipped in two, and the lesion reinforced in one. One patient had both anterior cerebral arteries clipped. Of the three patients who had clips applied proximal to the aneurysm, one recovered. The neck of an aneurysm distal to the anterior communicating trunk was clipped. This patient recovered. In this group, then, six patients (75 per cent) died.

Anterior communicating aneurysm. Anterior communicating aneurysms comprised 11 of this series. In six which were complicated by intracerebral hematoma, all patients died. The clots were removed in all. In one patient the aneurysm was clipped and packed with muscle; in another a muscle pack was applied and the extracranial carotid artery was ligated. In a third patient the anterior cerebral and anterior communicating artery was clipped and a muscle pack placed. In a fourth the aneurysm was not treated. In the fifth patient the intracranial carotid was clipped, and in the sixth the extracranial carotid alone was ligated. Three patients had clips applied to both anterior cerebral arteries, and in one the aneurysm was removed. Severe deterioration has persisted in the one recovered patient. In two cases the aneurysmal neck was clipped; one was reinforced with muscle. Both of these patients recovered without deficit. In the group of 11 patients with anterior communicating aneurysms, eight (78 per cent) died.

ANGIOGRAPHICALLY LOCALIZED ANEURYSMS

In reviewing our statistics, we found that, when aneurysms were localized angiographically and treated definitively, the mortality rate was considerably lower. The remainder of this report deals with only such cases. This group of patients was also reported by Hamby.[2]

Sixty-eight aneurysms are included in this series. Fifty-one of these were treated, with a mortality rate of 22 per cent, 15 deaths occurring in this group. For one or another reason, the remaining 17 patients were untreated. The mortality rate here was 65 per cent: 11 patients died in the hospital and one died at home from an apparent recurrent hemorrhage some six weeks following discharge from the hospital. The total mortality rate for the untreated group, then, is 74 per cent. In this latter group, eight patients were in too poor condition for operation and seven of them died. The one who lived had a recurrent hemorrhage, and angiography 13 days later revealed a middle cerebral artery aneurysm. Initial disorientation, irrationality, and a left hemiplegia persisted. After the mental state improved, operation was recommended but refused. Since further contact has not been possible with this patient, her condition is unknown. The total mortality in the combined treated and untreated group was 39.6 per cent.

Illustrative cases in this group of untreated patients are as follows: Three patients with demonstrable aneurysms had intracerebral hematomas removed. The aneurysm was not found at operation. We have considered these untreated from the standpoint of aneurysms.

One patient with four aneurysms demonstrated angiographically following a spontaneous subarachnoid hemorrhage is alive and well four years later. Another with a left supraclinoid aneurysm five days following subarachnoid hemorrhage had partial occlusion of the left internal carotid artery by a tantalum band. Seven days later the artery was completely occluded. About 20 hours following the occlusion, the patient suddenly became aphasic and hemiplegic. The band was removed. After many months the symptoms cleared and she recovered. She is well five years later, with a very mild aphasia and hemiparesis.

In one case, a patient with a left internal carotid aneurysm which had bled twice, partial occlusion of the internal carotid artery by a tantalum band was made extracranially. One and one-half hours later a right hemiparesis developed. The band was removed, the patient had bed rest for seven weeks, and was discharged asymptomatic. He is well five and one-half years later.

These latter two cases have also been considered untreated.

One patient had a small, asymptomatic calcific intrasellar tumor and a left middle cerebral artery aneurysm. She was not treated and died six weeks later of a subarachnoid hemorrhage.

In a patient with a bleeding left middle cerebral aneurysm, intracarotid pressure studies showed a reduction of 75 per cent of the original value upon occlusion of the common carotid artery. Treatment was delayed; on the following day the patient was hemiplegic and expired 24 hours later. Autopsy showed thrombosis of the left middle cerebral artery. There was no evidence of recurrent hemorrhage. The aneurysm had a well defined neck. Today we would attack such a lesion directly.

The last of these 17 untreated patients was a hypertensive woman with a bleeding anterior communicating artery aneurysm. Her hypertension was treated medically. She died suddenly two weeks following angiography from a recurrent hemorrhage from an aneurysm which had ruptured into the left frontal lobe and left lateral ventricle.

CERVICAL LIGATION

Of the 51 cases, 12 were treated by cervical ligation only and three (25 per cent) patients died.

We, like others, have found that operation within two weeks following subarachnoid hemorrhage carries a distinctly higher risk. In eight patients operated within the first week following the hemorrhage, there was fatality in six (75 per cent); one patient in five operated upon in the second week expired (20 per cent); two of 11 (18 per cent) expired when operated upon in the third week, one of four in the fourth week, and two of 15 (15 per cent) operated upon after the fourth week. In the first two weeks, then, there was a mortality of 55 per cent. After the second week, only four of 30 patients died, or 13 per cent.

The four deaths associated with operation after the second week require some comment. One patient had both anterior cerebral arteries occluded with resulting infarction of both frontal lobes; an associated pontine hemorrhage was found. A subdural empyema complicated operation in a second patient. In a third, a propagating clot developed from the site of a temporary intracranial carotid clip. In the fourth patient a carotid bifurcation aneurysm which ruptured during exposure was uncontrolled by a muscle pack. With better technics, these four deaths might have been avoided.

In the treated group, 43 (84 per cent) had previous subarachnoid hemorrhage; in the untreated group, 14 (82 per cent) had bled. Eight patients who had not bled were treated surgically and recovered.

POSTOPERATIVE FOLLOW-UP

Thirty-nine of 65 patients survived direct operation in the series, including those operated upon without angiography. A follow-up report was obtained from 38. Two patients had died, as previously recorded. One, who had lived normally for seven years following operation for a subclinoid aneurysm, died of a peritoneal sarcoma. The other had a preoperative hemiparesis without recovery and died of a perforated peptic ulcer four months after attack on a supraclinoid aneurysm. The longest follow-up was 11.5 years, the shortest six months, the average about eight years.

Twenty-six people survived operation for supraclinoid carotid aneurysms, including three at the carotid bifurcation. Three survivors had aneurysms on the infraclinoid carotid artery, two on the anterior cerebral, three on the anterior communicating, two on the middle cerebral, and two on the vertebral arteries.

Two of the three patients with bifurcation aneurysms are perfectly well and working daily without difficulty at their usual jobs; the other is hemiplegic.

Nineteen of the patients with supraclinoid lesions are doing the work they did before operation. One has a partial N-3 palsy. One recent patient is severely psychotic, one is totally disabled, and one attended college about a year ago and is now working with limitation. The last patient recovered from a preoperative bitemporal hemianopsia but was left with a postoperative hemiparesis.

In eight patients with extraocular nerve disturbance, there has been no further improvement in the deficit. Two patients with hemianopic defects improved following operation, but during the past one and one-half years no essential change in vision has been noted. The preoperative hemiparesis in one patient regressed completely; in another it is minimal. The three surviving patients with subclinoid aneurysms are at usual activity ten years, 11 years, and less than one year following operation. One patient still has a fixed pupil and optic atrophy.

Two survivors with anterior cerebral aneurysms are perfectly well. Of the three patients with anterior communicating aneurysms, two are neurologic cripples with profound frontal lobe disturbance. One was last heard from three years after operation, but could not be contacted this year. The third is fully recovered.

Two patients with middle cerebral aneurysms have shown no change. One still has a preoperative hemihypalgesia and hemiplegia; the other still has her preoperative convulsive activity. One patient with vertebral aneurysm continues to have disturbed balance and is not at work. He is now 65 years of age. The other patient, now 70 years old, is without complaint. These latter two aneurysms were actually untreated.

SURVIVORS WITH ANGIOGRAPHICALLY DEMONSTRATED ANEURYSMS

The survivors in that group of patients operated upon after angiography with definite localization of the aneurysms numbered 42. Nine of the 12 treated by carotid ligation lived. Two have died, one of a recurrent hemorrhage and the other of an unrelated cause. Two are asymptomatic. Three with mild neurologic deficits are working. One is mildly hemiplegic. The other could not be reached for follow-up.

We have summarized the results of the various methods of treatment of angiographically localized aneurysms in table 1.

Not included in this table because they were operated upon in another hospital are two patients who had aneu-

TABLE 1
RESULTS OF VARIOUS TREATMENT METHODS FOR ANGIOGRAPHICALLY LOCALIZED ANEURYSMS

	Carotid Ligation	*Trapping Operations*	*Aneurysm Neck Clipped*	*Reinforcement*	*Total*
Total cases	12	18	20	1	51
Surgical fatality	3 (25%)	4 (22%)	4 (20%)	0	11 (21.5%)
Surviving operation	9	14	16	1	40
Status unknown	1				1
Well	2	5	9		16
Working, with mild neurologic deficits	3	6	3		12
Considerable neurologic deficit	1	2	3	1	7
Invalid		1	1		2
Subsequent death	1 hemorrhage 1 unrelated	1 unrelated			3

rysms treated by intracranial and extracranial carotid artery trapping procedures. One patient had a preoperative right homonymous field defect with improvement in vision. There were also an additional five with extracranial carotid ligation. Two with supraclinoid carotid lesions have made incomplete recovery from N-3 palsy and first division trigeminal pain. One with a subclinoid carotid aneurysm, with an incomplete N-3 palsy, has made an incomplete recovery of extraocular muscle function. Another, with a supraclinoid aneurysm with subarachnoid hemorrhage, had a postoperative left hemiplegia which has improved. The last patient died some 24 hours following carotid ligation, autopsy revealing a propagating clot from the site of the ligation. All of these patients were operated upon eight years ago.

COMMENT

In addition to surgical technic, other factors also determine the ultimate mortality rate in the surgical treatment of intracranial aneurysms: the presence of an associated destructive intracerebral hematoma, the time interval between subarachnoid hemorrhage and operation, and planned operation following exact localization of the aneurysm by angiography.

Fourteen (66 per cent) of the 21 patients whose aneurysms were not angiographically demonstrated died; of these 14, the aneurysm was not treated in six.

In a total of 75 angiographically demonstrated aneurysms, 58 of which were treated by planned operation, the total mortality was 20.7 per cent (12 patients). In the direct attack on angiographically demonstrated aneurysms, the mortality was 19.5 per cent.

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■ To understand fully the mode of influence of the nervous system, in health and disease, upon nutrition, secretion, and animal heat, it is necessary to distinguish clearly the effects due to this influence from those due to its absence. Although these two kinds of effects are very different one from the other, they have very often been confounded. For instance, it might be easily shown that many of the best writers on physiology and pathology, when trying to prove that an influence of the nervous system is necessary to nutrition and secretion, bring forward facts showing the effects of excitation of the nervous system, together with facts depending upon the absence of action of this system.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Ultrasound in Neurology

William J. Fry

THE CHANGES produced in nerve tissue resulting from intense ultrasonic irradiation under controlled dosage conditions have been described in detail in a number of publications from this laboratory.[1–4] This paper is concerned with a discussion of the microscopic selectivity and a description of the instrumentation and the technic of irradiation of the animal. The types of lesions which can be produced are illustrated with low power photographs of stained tissue sections and instrumentation and technic of irradiation[5] are discussed.

The focussed ultrasonic multiple beam method of producing lesions in the central nervous system constitutes a considerable advance over the older procedures for destroying tissue. Changes can be produced at any desired depth without damaging intervening tissue. The selectivity, which under proper ultrasonic dosage conditions can be realized in the lesion region, is not attainable by any other method demonstrated up to the present time, and it provides an entirely new approach to many neurologic problems. The fact that all neural components in a given region can be destroyed without interrupting the blood vessels in the same region completely eliminates the difficulties inherent in older procedures, namely the spread of the lesion to regions supplied by interrupted blood vessels which traverse the site of the primary lesion. Since white matter is more readily affected by ultrasound than gray matter, it is possible to completely destroy nerve fiber tracts bordering or surrounded by nerve cell body regions without damaging the tissue of the gray matter, that is to say, the practically complete prevention of invasion of a lesion into gray matter can be readily attained. Consequently, any complex-shaped fiber tract can be destroyed without encroaching on neighboring gray matter. Lesions can, of course, be produced in gray matter by increasing the ultrasonic dosage over that required to produce lesions in the white matter. In addition to the selectivity already mentioned, which can be readily realized, evidence exists which indicates that, under certain ultrasonic dosage conditions, nerve fibers in both white and gray matter can be demyelinated without destruction of the axis

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cylinders. Such naked axis cylinders have been observed microscopically four days after irradiation. The ultimate fate of these axis cylinders is not known at the time of writing of this paper. Precise positioning, small size (as small as 1 to 2 cubic millimeters), and accurate reproducibility of lesions are consistently obtained with a suitably designed instrument yielding precisely controllable dosages. In addition, the procedure is well tolerated by the animals so that treatment mortality can be kept very low.

Extensive histologic studies of the ultrasonically produced selective lesions have been accomplished. Histologic preparations of the brains of over 300 ultrasonically-irradiated cats and monkeys have been examined in the course of this study, in which the time course of the development, the degree of selectivity, and the accuracy of localization have been investigated. This ultrasonic method is being applied in this laboratory for neuroanatomic and neurophysiologic studies on experimental animals. Preparations for application of this method to human neurosurgery are in progress.

The term "ultrasound" refers to sounds whose frequencies are above the range of human audibility (human audible limit is 15,000 to 20,000 cycles per second). Since the velocity of propagation, V, of sound waves in a fluid medium is practically independent of the frequency and since the propagation velocity is equal to the product of the frequency f and the wavelength λ ($V=f\lambda$), it is evident that the higher the frequency the shorter the wavelength. A short wavelength is necessary for this work since the minimum focal spot size which can be produced is proportional to the wavelength. Thus, if a focal spot size of the order of two millimeters in diameter is desirable, it is necessary to use sound waves with a frequency in the neighborhood of a million cycles per second or higher. At a frequency of a million cycles per second, the wavelength of the sound in physiologic saline and soft tissue is about 1.5 millimeters (velocity of sound propagation in saline is about 1,500 meters per second). The sound waves can be focussed by a lens in a fashion similar to that used for visible light. Such a focussing device is illustrated schematicaly in figure 1. The sound is produced by an element E (such as a quartz crystal plate) which is excited electrically to vibrate at resonance (vibration consists of an alternating change in thickness of the element). The sound traverses medium M

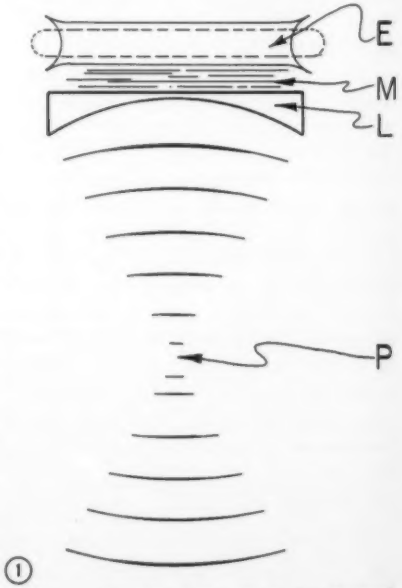

FIG. 1. Focussing system (lens) for ultrasound. For description of symbols see text.

and passes through the plano-concave lens *L*, which focusses it at *P*. Four of these focussing devices can be combined into one unit as illustrated by the irradiator shown in figure 2. The four individual focussed beams can be brought into coincidence by adjustments provided on the irradiator. This focussed multiple beam irradiator has been used to produce the types of localized selective lesions discussed in this paper.

FIG. 2. Four beam focussing ultrasonic irradiator.

It is not practical to increase the frequency indefinitely in order to obtain smaller and smaller focal spot sizes if the beam must penetrate much tissue before coming to a focus. This limitation is imposed by the fact that the absorption of the sound by the tissue increases as the frequency increases. The sound level must consequently be increased at the port of entry into the brain to offset the absorption losses which occur along the transmission path. The losses may become so great at higher frequencies that the increased sound level required would result in damage to the brain where it enters and along its transmission path. A frequency of one million cycles per second is about the maximum practical if the sound must penetrate the maximum depth of a human brain before coming to a focus to produce a lesion.

Even in the one million cycle per second frequency range, the absorption in bone is so great that it must be removed to prevent damage to adjacent nerve tissue caused by flow of heat from the bone to the soft tissue. However, there is an additional reason for removing the bone overlying the surface of the brain at which the sound is to enter, namely, the sound propagation velocity in bone is quite different from its value in brain tissue. Therefore, the sound beams would be distorted if they traversed the skull bone prior to being focussed in the brain. The removal of the bone eliminates the difficulty of distortion and the sound can then be conducted from the lenses to the exposed dura through sterile physiologic saline. Since the acoustic levels used are quite high, it is necessary to degas the saline before using it to prevent the formation of bubbles in the transmission path. Degassing can be accomplished by boiling for a few minutes and then cooling.

The physical mechanism of the action of the sound on the tissue is not understood at the present time, although it is clear that the primary effect is not the result of heating. That the action is not the result of temperature changes resulting from the conversion of acoustic energy into heat has been demonstrated

in a number of ways. Experiments on cooled animals, in which the increased temperature due to the sound never exceeds a "normal" temperature for the animal, demonstrates this convincingly.[6] Additional evidence for this viewpoint is the fact that sound pressure amplitude or sound particle velocity amplitude is more simply related than sound intensity to the exposure time necessary to produce a specified effect on the central nervous system.[7] The time rate of heating produced by passage of the sound through the tissue is directly proportional to the acoustic intensity for a progressive wave (no standing waves). The sound pressure amplitude is a measure of the fluctuating or alternating pressure in the medium resulting from the passage of the acoustic waves. The particle velocity amplitude is the maximum value of the alternating speed of the particles of the medium during passage of the sound waves. Greater intensities correspond to larger alternating pressure and particle velocity amplitudes, and these two latter quantities are in fact directly proportional to the square root of the intensity in a plane progressive wave. As a result of the fact that the pressure and/or particle velocity are probably more basic in the mechanism of the action of the sound on the tissue than is the intensity and since values for the space distribution of intensity do not completely describe the acoustic field conditions in a sound field of the type produced by the multibeam focussing

FIG. 3. Irradiation room.

irradiator, the ultrasonic dosage conditions are stated in terms of the frequency, pressure amplitude, particle velocity amplitude, and duration or durations of exposure. To complete the description, it is also necessary to note that the sound level rises to its maximum value at the initiation of exposure and falls to zero from its maximum value at the termination of exposure, in a time which is very short compared with the duration of exposure.

The technic of preparation and irradiation of the subject and the apparatus for control of dosage and localization will now be described. The specific machine to which the description given here applies is the prototype instrument for human ultrasonic neurosurgery. This equipment is housed in a double room arrangement; the subject is irradiated in the lower room (figure 3) and the positioning system is housed in the upper room (figure 4). The electrically shielded irradiation room contains apparatus for supporting the animal, calibration instrumentation for determining the acoustic output of the transducers, and controls for positioning the focused ultrasonic beams, as well as stimulators, amplifiers, oscilloscopes, cameras, and other recording devices for observing electrical activity of central nervous systems during irradiation. Projecting through the ceiling of this room is a metal tube (10 feet long and 7 inches in diameter) which supports the focussing transducer. The precise positioning of the sound

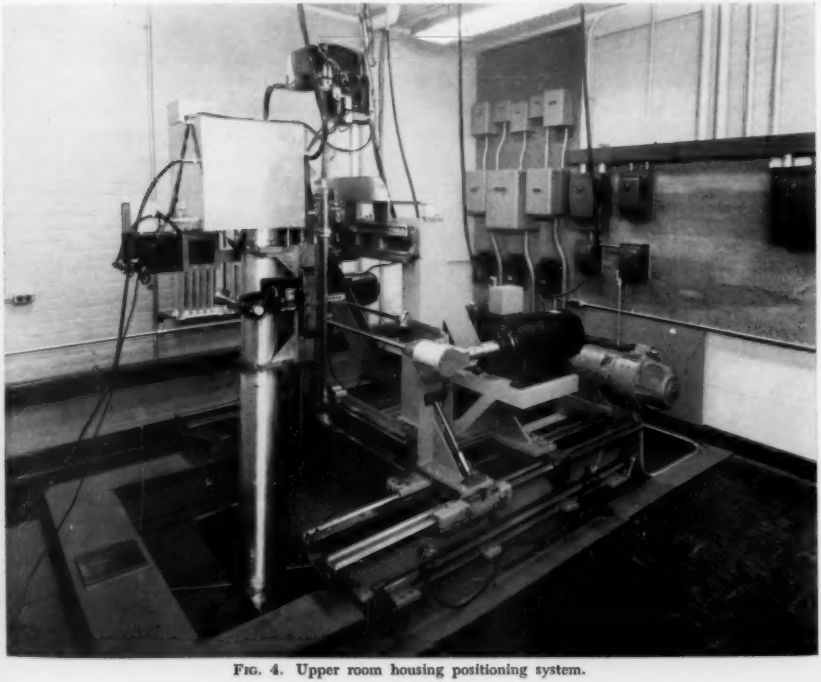

FIG. 4. Upper room housing positioning system.

beam is accomplished by the motor driven positioning system which supports the transducer. This system permits translational motion in three mutually perpendicular directions and also two rotational motions. The positioning system itself, which weighs about 3,500 pounds, is mounted on a steel girder framework in the upper room directly over the irradiation room. The controls for this system are placed in the irradiation room below. This instrumentation makes possible accurate localization of the acoustic radiation in any desired region of the central nervous system under precisely controlled dosage conditions.

Previous to preparing the animal, one calibrates the multibeam irradiator at the focal spot by choosing a convenient voltage to electrically excite the vibrating elements. An acoustic probe, which makes possible relatively rapid accurate determinations of the acoustic variables, pressure amplitude, and particle velocity amplitude, has been especially developed for this purpose.[8,9] Both the probe and the irradiator are immersed in a calibration tank filled with salt water for the calibration procedure. The exciting voltage corresponding to the sound level desired (pressure amplitude, particle velocity amplitude) at the site of the lesion is determined. Absorption losses in the thickness of brain tissue between the port of entry and the focal region are taken into account in this determination.

To produce a precisely localized lesion by ultrasound, the head of the anesthetized animal (cat, monkey) is engaged in a stereotaxic substructure in which the usual interaural, Frankfort, and midsagittal planes are employed as "zero-references." Before the animal is placed in the apparatus, a pointer attached to the irradiator and coinciding with the focal spot of the irradiator is positioned on the midline of the stereotaxic apparatus and is collinear with the line through the bars which support the skull of the animal at the ears. The coordinate values on the system that supports the irradiator are read corresponding to this ear-bar "zero." One can then transform from the coordinates ordinarily used with the stereotaxic apparatus to the coordinates of the system supporting the irradiator. The pointer is then removed from the irradiator and the animal is mounted in the machine. The soft tissues are incised over the appropriate area of the brain and the skull cap is removed. The dura mater need not be opened. At this point of the procedure, no definitive surgical measures beyond those of achieving hemostasis are required.

The next step consists of attaching the skin of the animal to a special flanged hopper in such fashion as to provide a "pan," the bottom of which consists of the exposed dura mater. This "pan" holds

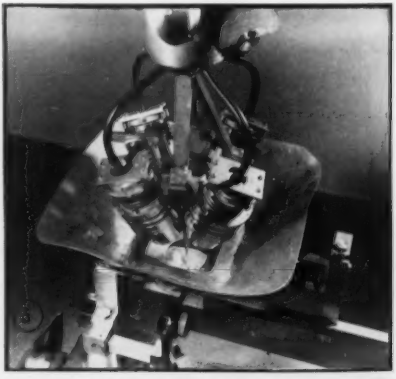

FIG. 5. A view from above showing the arrangement of irradiator, pointer, pan, skull, and head holder.

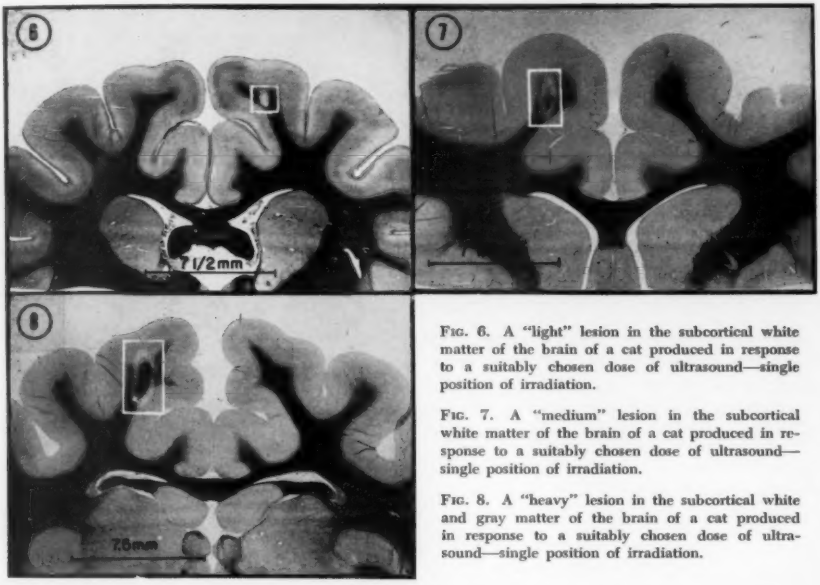

FIG. 6. A "light" lesion in the subcortical white matter of the brain of a cat produced in response to a suitably chosen dose of ultrasound—single position of irradiation.

FIG. 7. A "medium" lesion in the subcortical white matter of the brain of a cat produced in response to a suitably chosen dose of ultrasound—single position of irradiation.

FIG. 8. A "heavy" lesion in the subcortical white and gray matter of the brain of a cat produced in response to a suitably chosen dose of ultrasound—single position of irradiation.

the degassed physiologic saline which acts as the transmitting medium for the sound. The arrangement of the irradiator, pan, head holder, and skull of the animal are illustrated in figure 5. The pointer, the function of which is discussed above, is shown in the lowered position.

The sterilized multibeam irradiator, which is supported and moved about by the carriage unit (figure 4), is then positioned in the saline medium at the position or positions required to place the focal spot of the irradiator in the region in which a lesion is to be produced. For the smallest lesions the tissue is irradiated with the focal spot in single isolated positions, but for larger lesions the focal spot is placed successively in a number of adjacent overlapping positions. After exposing the brain to the proper ultrasonic dosage in the desired number of positions, the animal is returned to the operating room where closure of the cranial muscles and scalp is accomplished. This surgical procedure may also be performed in the irradiation room, since the apparatus is designed so that the tube which supports the irradiator can be retracted sufficiently to permit the implementing of standard operative procedures below it without interference.

The animals are observed for periods varying from minutes to months following exposure, during which time physiologic and/or psychologic aberrations may be noted. The animals are then sacrificed, and the brains removed, fixed, sectioned, and stained.

It is possible to illustrate some of the important characteristics of the ultrasonic method of producing lesions in the central nervous system by low power

photographs of stained tissue sections. If the subcortical white matter of the brain of a cat is irradiated in a single isolated position, a lesion of the type illustrated in figure 6 is produced when the dosage is just above that required to produce a minimal effect. The lesion area (the maximum cross section is exhibited in the section illustrated) possessess a relatively homogeneous field of necrosis two hours after irradiation and there is no invasion of the neighboring gray matter. This lesion, which is about one millimeter in maximum diameter, possesses extremely sharp boundaries which are characteristic of these ultrasonic lesions. As the ultrasonic dosage is increased, the lesion (figure 7) exhibits a central region which stains more nearly like normal tissue than the peripheral necrotic region, even many hours after irradiation. (See reference 4 for a complete tabulation of the time sequence of the tissue changes in both white and gray matter following various graded dosages of ultrasound.) Even at such a dosage, however, the gray matter bordering on the lesion area is unaffected and a sharp boundary between the affected white matter and the neighboring gray matter is apparent. As the ultrasonic dosage is further increased, the gray matter becomes affected and a lesion such ast that shown in figure 8 is obtained. The dosage used in producing the lesion illustrated was sufficiently high that the gray matter was directly affected. Graded series of lesions of the type just illustrated are produced by ultrasound at 50 atmospheres acoustic pressure amplitude, 450 centimeters per second particle velocity amplitude, and durations of irradiation (single exposure) in the range from 1.00 to 2.00 seconds. The sharp boundaries characteristic of these ultrasonic lesions are present in both the white and gray matter, and the central darkstaining region in the white matter portion of the lesion is quite apparent at this heavy dosage. Even at this heavy dosage blood vessels which enter and are present in the lesion region are not interrupted. It is of interest to note here that even for a heavy dosage, such as that used to produce the lesion illustrated in figure 8, the changes in the tissue are not apparent under the microscope for about ten minutes after irradiation. The first change which is observed is a slight destaining,

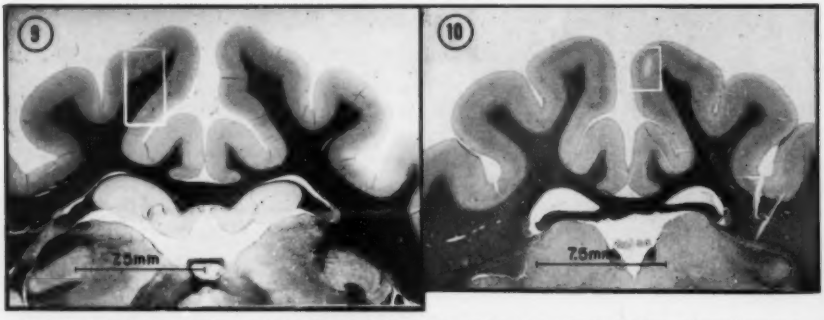

FIG. 9. The initial histologic change observed 12 minutes after ultrasonic irradiation—"heavy" lesion.
FIG. 10. An ultrasonic lesion in the midline cortical gray matter of a cat brain.

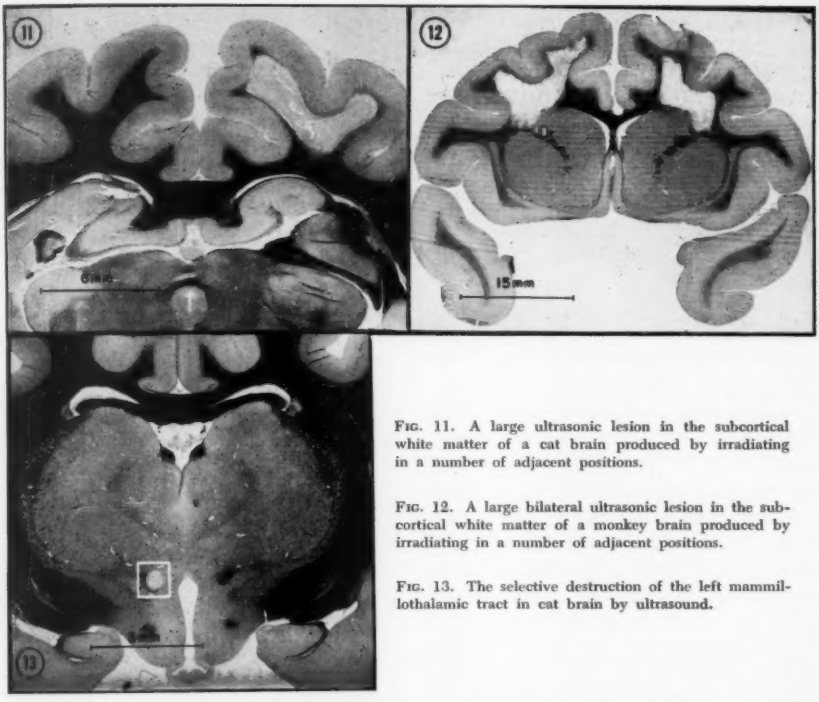

FIG. 11. A large ultrasonic lesion in the subcortical white matter of a cat brain produced by irradiating in a number of adjacent positions.

FIG. 12. A large bilateral ultrasonic lesion in the subcortical white matter of a monkey brain produced by irradiating in a number of adjacent positions.

FIG. 13. The selective destruction of the left mammillothalamic tract in cat brain by ultrasound.

which becomes evident for heavy lesions about ten to 15 minutes after exposure. This is illustrated in figure 9, in which the change is more apparent in the gray matter than in the fiber tracts. A lesion can, of course, be restricted entirely to gray matter by suitable positioning of the focal region of the beams in the tissue (figure 10). As indicated previously, the ultrasonic dosage required to produce changes in gray matter is greater than that required for white matter changes. Therefore, if it is desirable to destroy a gray matter region without disrupting bordering white matter, the focal region of the beam must be positioned geometrically with respect to the border between the gray matter and the fiber tract so that the white matter is not subjected to the high sound level used to affect the gray matter. A graded series of lesions can be produced in gray matter by irradiating the tissue at the pressure and particle velocity amplitudes given above for white matter, but with the duration of exposure in the range 2.00 to 3.00 seconds.

All of the lesions illustrated so far were produced by irradiating the tissue with the focal spot of the ultrasonic beams in a single position. Since it is possible to destroy fiber tracts without disrupting neighboring gray matter by proper dosage control, one can destroy practically any complex-shaped white matter region of any size without dis-

rupting cell body regions which border on the region to be affected. Such large size complex-shaped lesions are illustrated in the next two figures. The stained tissue section shown in figure 11 illustrates a large subcortical white matter lesion produced by irradiating the tissue (cat) with the focal spot of the ultrasonic beam placed successively in a number of positions spaced 0.5 millimeter apart. Sharp boundaries are exhibited by these large lesions and the gray matter which borders on the lesion area is not affected, even though it receives exactly the same ultrasonic dosage as the neighboring fiber tracts which are completely destroyed. The blood vessels in a lesion as large as this one are still functional after irradiation, that is, no interruption of blood flow is produced by the sound. Another example of a large shaped white matter lesion is illustrated in figure 12. This tissue section is taken from the brain of a monkey irradiated bilaterally at a large number of positions (52) at a dosage sufficient to destroy the fiber tracts of the white matter without disrupting the gray matter. The shaping of the lesion around both the cortical gray and deep nuclei is clearly shown. The brain was irradiated with the focal spot of the beams spaced one millimeter apart at adjacent positions. The brain became slightly distorted on imbedding and consequently the white matter in the superior frontal gyrus of the right side does not appear completely disrupted in the tissue section illustrated. However, examination of serial sections indicates that the white matter was completely disrupted in the superior frontal gyrus on this side also. The brain was irradiated to within 1.5 millimeters of the midline at the level of the subcortical white matter of the superior frontal gyrus, but at the deeper levels the tissue within 6.5 millimeters of the midline was not irradiated. This is clearly shown in the tissue section, that is, the white matter of the cingulate gyrus is not disrupted. It is of interest to note that the ultrasonic dosage chosen to produce this lesion was based on a knowledge of the dosage required to produce such selective lesions in cat brain. It is thus apparent that a dosage study based on cats is sufficient to serve as a criterion for the selection of dosages for monkeys. It is, therefore, expected that the dosages required to produce selective lesions in human beings would not be greatly different.

The next three figures illustrate the accuracy of localization in the selective destruction of the whole or a part of a small deep fiber tract. This is illustrated by ultrasonic lesions produced in the mammillothalamic tract of a cat. This tract, which is about one millimeter in diameter and is at a depth of four-fifths of the total brain thickness, constitutes a convenient test object on which to demonstrate the potency of the ultrasonic method. Ultrasonic lesions have been produced in the mammillothalamic tracts of 34 cats. Single position irradiation was used. In the lateral coordinate direction, 90 per cent of these lesions fall within $\pm$ 0.5 millimeter of the desired position, and in the anterior-posterior direction 75 per cent of the lesions are within $\pm$ 0.5 millimeter of the desired anatomic locus. The vertical positioning does not constitute a test of placement accuracy in this series, since the focal region of the beam was oriented with its axis along the vertical direction. Therefore, since the length of the focal region (5 millimeters with a

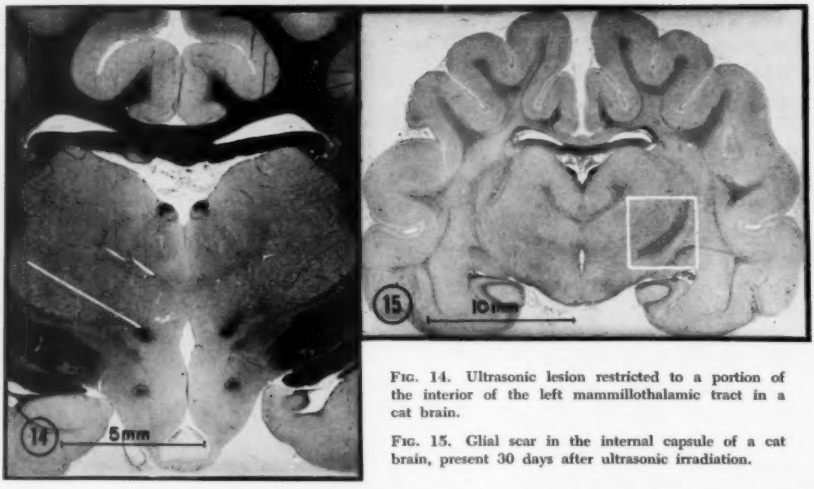

FIG. 14. Ultrasonic lesion restricted to a portion of the interior of the left mammillothalamic tract in a cat brain.

FIG. 15. Glial scar in the internal capsule of a cat brain, present 30 days after ultrasonic irradiation.

particle velocity amplitude equal to or greater than 90 per cent of the maximum value) of the beam is several times greater than its diameter (0.8 millimeters with a particle velocity amplitude equal to or greater than 90 per cent of the maximum value), there was no difficulty in hitting the tract every time as far as the vertical position was concerned. The numerical values quoted for placement uncertainty include, of course, the variation in the position of the structure (mammillothalamic tract) with respect to the external reference landmarks on the skull which are used in positioning the head of the animal in the holder.[10] Since the dosage was chosen to selectively destroy the tract without disrupting the surrounding gray matter, the variation in position is exhibited as a lesion in which the tract is only partially destroyed. In figure 13 the left mammillothalamic tract is essentially completely destroyed. Figure 14 exhibits a lesion in the interior of the tract. In this last example, the effective size of the focal region of the beam to produce a lesion was so small that only a small portion of the interior of the tract was destroyed. The stained tissue sections of the figures show the maximum size of the lesion in each case. Microscopic examination of the tissue between the mammillothalamic tract on which the ultrasound was focussed, and the port of entry of the sound into the brain (cerebral cortex) shows no tissue changes anywhere along the transmission path.

The mammillothalamic series of lesions, examples of which are illustrated here, was produced to determine the accuracy of placement of a single tiny ultrasonic lesion within the deepest portion of a cat brain. The series also furnishes material for an anatomic study of this tract, its course, and terminations. If the severing of the entire tract in essentially every animal were the objective, without disturbance to neighboring gray matter, this could be readily accomplished by irradiating with the

focal spot of the sound beams placed successively in a number of positions to cover a region which includes the total space variation of the tract with respect to the external landmarks. The ultrasonic dosage delivered at each position would, of course, be chosen so that the radiation does not affect gray matter.

Large lesions of almost any desired shape can be produced in fiber tracts in the depths of the brain. The tissue section of figure 12 illustrates a lesion in the brain of a monkey which has a lower border following the boundaries of the gray matter masses at intermediate depth. The tissue section of figure 15 shows a glial scar which has formed and is present 30 days after the production of a crescent-shaped lesion in the deep fiber tracts of the internal capsule of a cat brain. This lesion in the capsule was produced by irradiating the tissue in a number of positions with beam centers spaced 0.5 mm. apart.

From the work that has already been accomplished, it is clear that the ultrasonic method of producing accurately localized selective lesions in the central nervous system constitutes a new and powerful tool for experimental neurology and it has considerable potential value for neurourgery.

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Bilateral Carotid Artery Obstruction

Edwin Clarke, M.D., M.R.C.P. and C. V. Harrison, B.Sc., M.D.

In 1896 Hutchinson[59] pointed out that clinicians and pathologists alike frequently neglect to examine the carotid arteries. Chiari,[20] Hunt,[58] and Saphir[96] made similar observations, but it is only in the last decade that the clinical significance of internal carotid artery occlusion has been adequately realized.

The clinical picture of unilateral involvement is now widely recognized, but the results of bilateral obstruction are less well known. The outcome of the latter occurring suddenly has been popular knowledge since before the time of medical records, and Valverdus[112] described how in 1544 the anatomist Columbus demonstrated it publicly in Pisa. The effects of a chronic obliterative process are, however, more obscure. It is important to note that Fisher[44,45] has suggested that they may be confused with those due to a primary cerebral disease characterized by mental changes; in addition he believed that treatment in such cases may not be impossible. We propose to evaluate these observations, making use of two cases and those in the literature.

Case 1. A housewife aged 67 entered the hospital on February 5, 1954 and died there nine days later. She could give no reliable information and details of her illness were obtained from relatives. For five years mental changes had been present but they had become more marked in the previous two years. She had periods of depression which alternated with outbursts of temper, quarrelling, and sharp-tongued criticisms that greatly embarrassed visitors. She became irresponsible concerning money, squandered her savings, and could not manage her shopping. A marked defect of recent memory became obvious and she began to drink, a custom that had not been present previously. She lost all interest in her surroundings, became embittered and intolerant of those around her, and finally confined herself to a room where both she and its contents degenerated into an apalling state of filth and neglect. She had complained of recent vague limb pains, anorexia, and constipation. Her legs felt heavy and walking had deteriorated to a clumsy shuffle.

At the menopause when she was 53 years old, she had suffered a depressive episode but otherwise had experienced no illnesses of note. A sister had lost the sight of the right eye suddenly, followed by partial blindness in the left and then by a right hemiparesis. Another sister had suffered the same ocular symptoms.

On examination elsewhere on December 5, 1953, she was found to be dull and confused. The nervous system was normal and it was thought that her condition was a "functional" one. Blood count and serum electrolytes were normal and the blood Wassermann reaction was negative. The blood sedimentation rate was

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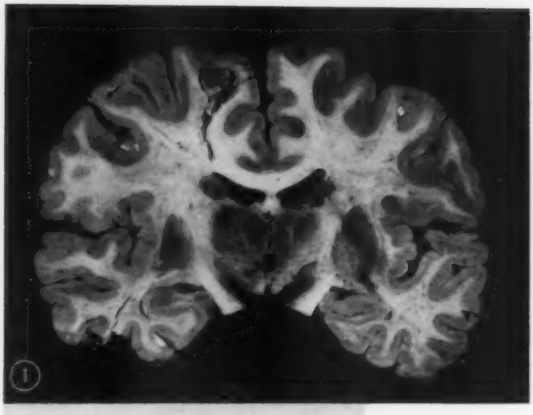


FIG. 1. Cross section of brain showing cerebral atrophy and softening in the distribution of the right anterior cerebral artery.
FIG. 2. View of sella turcica from above, showing distal portions of internal carotid arteries with pinhole lumina anteriorly.

15 mm. (Wintrobe, corrected) and two weeks later it was 31 mm. She fell on January 23, 1954 because of leg weakness; the cerebrospinal fluid which was examined at this time was normal and the Wassermann reaction negative.

Examination. Her general condition was poor. The main content of her spontaneous conversation was a tearful and vague account of her complaints. Direct questioning, however, produced garbled and confused statements without fabrication. She was depressed and her attention fluctuated so that cooperation was poor and concentration inadequate. She evaded questions concerning local topography and contemporary events and was considerably disoriented. Her performance of the simpler psychometric tests was very poor. She had occasional visual hallucinations, the most persistent being that of flies crawling on her dentures.

The retinal vessels were arteriosclerotic and visual acuity seemed reduced. She was reluctant to move the left arm and its power was slightly reduced. There was moderate weakness of the left leg. All the limbs were stiff and there appeared to be a mixture of pyramidal and extrapyramidal types of change in tone. This was more marked in the legs, especially the left. All the tendon reflexes were symmetrically enhanced, the abdominal reflexes were absent, and the plantar responses extensor; there was a pronounced left grasp reflex and a less obvious one on the right. Although she was a very poor sensory witness, there appeared to be a defect of stereognosis in the left hand and impaired joint position of the left big toe. A soft systolic murmur was heard at the aortic area and the blood pressure was 170/85. The peripheral vessels were all pulsating normally. The internal carotids were readily palpable, both in the neck and in the tonsillar fossae.

Progress. She gradually became more demented, although the physical signs did not change, and eventually she was incoherent and

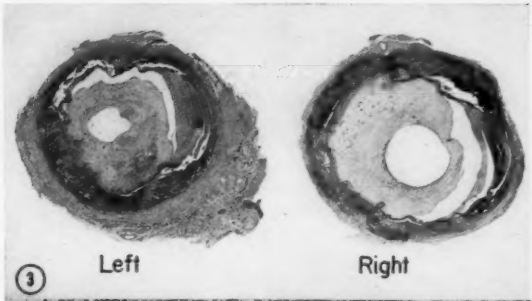
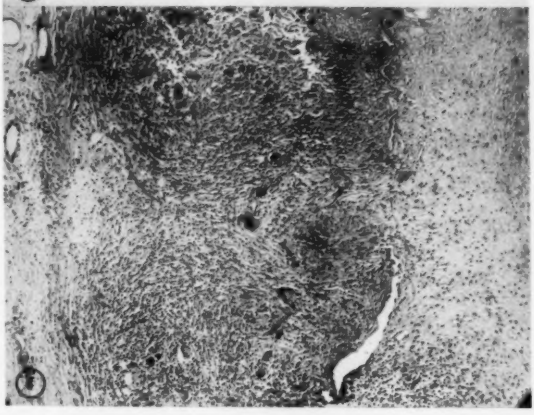


FIG. 3. Transverse sections of the internal carotid arteries at comparable levels near their emergence from the cavernous sinus. The lumina are greatly reduced by intimal thrombosis and there is tearing due to calcareous atheroma (hematoxylin and eosin stain).

FIG. 4. High-power view of right internal carotid artery. On the right there is intimal fibrosis, and bordering it is the fragmented internal elastic layer. The media is necrotic in the upper part and everywhere heavily infiltrated with inflammatory cells. Numerous giant-cells are obvious. Thickened adventitia is on the left (hematoxylin and eosin stain).



inarticulate. Signs of an acute pulmonary infection appeared and, despite treatment with antibiotics, she lapsed into coma and died on February 14, 1954.

Autopsy. The cause of death was purulent bronchitis. In addition, a left double ureter, an acute duodenal ulcer, and small myomata of the uterus were found. The heart was healthy and both coronary arteries and aorta were remarkably free from atheroma.

Brain: 1) Macroscopic appearances. Formol-saline was perfused through the common carotid arteries and following this the brain weighed 1,160 gm. Moderate atrophy was noted externally, mainly in the frontal regions. On section, the atrophy was confirmed and furthermore there was an area of recent softening in the right parasagittal region (figure 1). *2) Microscopic appearances.* There were none of the appearances that characterize the presenile dementias[101] and Bielschowsky's stain demonstrated the absence of senile plaques. The area of softening was confirmed.

Carotid arteries: 1) Macroscopic appearances. In the neck the internal carotid arteries were healthy, but on entering the cavernous sinus they rapidly narrowed, then regained their normal diameter on entering the intracranial cavity. The degree of narrowing is shown in Figure 3, the right artery having a luminal diameter of 1.3 mm. and the left 0.75 mm. after fixation in the distended position. Figure 3 does not necessarily depict the vessels at the site of the maximum obstruction and it is certain that very little blood could be transmitted by them. The thickening of the arterial wall was white and fibrous rather than yellow, and at first it was thought to be due to old thromboses. The basal arteries of the brain were strikingly free from atheroma, and and this was also true of the anterior, middle, and posterior cerebral vessels. The circle of

Willis, however, showed two abnormalities (figure 5); the right posterior communicating artery was rudimentary, with little or no lumen, and the origin of the left anterior cerebral artery was similarly affected so that both anterior cerebrals were being fed almost exclusively by the right internal carotid artery. There was no antemortem clot in the carotids or basal vessels. *2) Microscopic appearances.* The narrowed segments of the internal carotid arteries were cut into serial segments, which were embedded and sectioned. On examination, there were two independent lesions. First there was old atheroma with fibrous intimal thickening and calcification. In addition, a more recent fibrous intimal thickening of looser texture was present. At every level of the arteries there was an active arteritis affecting the media, sometimes the whole circumference, but more often only part. The cellular reaction was dominated by macrophages and lymphocytes, except in necrotic areas where polymorphonuclear cells were seen. The internal elastic lamina was fragmented, often into short irregular lengths. Giant-cells were relatively frequent and were often found in relation to fragmented elastic tissue. The adventitia showed fibrous thickening, but only slight and diffuse lymphocytic infiltration (figure 4).

The arterial lesions had all the characteristics of a giant-cell arteritis. The external carotid arteries and those examined in the brain and elsewhere in the body showed no evidence of these changes.

Comment. The clinical diagnosis in this case was difficult. Terminally the association of dementia, pyramidal, and extrapyramidal signs suggested the Jakob-Creutzfeld syndrome. The area of softening in the distribution of the right anterior cerebral artery partly accounted for the left-sided limb signs, but the bilateral features indicated involvement of both cerebral hemispheres. Dunning[31] has reported the value of carotid palpation in the tonsillar fossa, but despite distal blockage, the arteries of our patient could both be felt to pulsate. Gurdjian and Webster[51] have also questioned the reliability of this procedure. The remarkable family history remains unexplained because further information could not be obtained. It is of interest to note, however, that Beevor and Gunn[8] and Frövig[47] have described a similar familial condition. The association of atheroma and giant-cell arteritis is known,[17] but it is difficult in our case to make a clinicopathologic correlation between length of history and the duration of the disease process.

If this case be included, there are 69 adequately recorded examples of bilateral carotid artery occlusion. Only those with incontrovertible evidence of complete or virtually complete carotid obstructions (as in case 1) have been accepted. The case of Baillie,[4] together with those of Saphir,[96] Zillig,[116] Fisher,[44] Martelli,[66] and eight of the cases reported by Currier, DeJong, and Bole[24] have been excluded because adequate evidence of effective bilateral arterial blockage was not available. Marx[67] gave no clinical information concerning his case and it, in common with acute cases such as that of Paillas and Bonnal,[80] has been excluded.

PATHOLOGY

The pathologic processes in 62 cases are shown in table 1; in seven they are unknown. Although there was longstanding arterial disease in all cases, in some instances complete bilateral occlusion occurred only shortly before death due to impaction of an embolus.

Pulseless disease was present in 60 per cent of those with known pathology, and in each case the common carotid arteries, together with other branches of the aorta, had been occluded by a primary aortic disease ("pulseless disease"—Shimizu and Sano[100]). The commonest etiologic agent was syphilis, but in

TABLE 1
PATHOLOGY AND MENTAL CHANGES IN 69 CASES OF BILATERAL CAROTID ARTERY OBSTRUCTION

Pathology of Obstruction	Mental Changes		No Mental Changes	Totals
	Severe	Mild		
Pulseless disease	0	6	31	37
Atherosclerosis	5	4	10	19
Giant-cell arteritis	1	1	2	4
External pressure	0	1	0	1
Thromboangiitis obliterans	0	0	1	1
Unknown	1	1	5	7
	7	13		
	20		49	69

some[52] a nonsyphilitic arteritis, presumably similar to the primary arteritis of the aortic arch described by Barker and Edwards,[5] was found. Currier and coworkers[24] have collected the cases of pulseless disease with neurologic manifestations, but those of Pilz,[86] Fahr,[37] and Cooley and McNamara[23] must also be considered; eight cases can be rejected because carotid obstructions were not sufficient bilaterally. The careful study of Frövig[47] and Frövig and Löken[48] exemplifies this type of case, although the cases of Deville[26] and Guinard[50] cited by these authors are not acceptable.

Atherosclerosis occurred in 31 per cent, being present in all of Fisher's[44,45] cases. The commonest site for atheromatous obstruction of the internal carotid artery is in its proximal portion, the carotid sinus.[57] Atheroma may, however, occur in the terminal part of the artery, and Dow,[29] Dörfler,[28] Saegesser and Tchicaloff,[94] and Meyer and Beck[70] have indicated the frequency and extent of such lesions. Duff and McMillan[30] and Blumenthal, Handler, and Blache[11] pointed out the importance of local and mechanical factors in the production of atheromatous plaques, and the tortuosity of the internal carotid artery within the cavernous sinus is itself a potent factor.[115] Examination of the terminal part of the vessel has often been neglected[20,45] but Samuel[95] has shown that atherosclerotic lesions of it are commoner than is believed at present. The cases of Peacock and Bristowe[81,82] were probably of this type.

Giant-cell arteritis affects arteries other than those of the cranium,[92] and 12 cases with internal carotid involvement have been reported. In only three (6 per cent of the 62 cases), however, was it bilateral and sufficient to reduce the lumina significantly.[49,69] Our case is a further example and, like those of Gilmour,[49] the lesions were in the carotid syphon. The cases of Barnard[6] and Ritama[91] had similar lesions, but occlusion was incomplete and information inadequate. It is remarkable that in our patient the disease was restricted to the internal carotid artery and that in particular the external carotid system had not been affected. The explanation for this localization is not apparent, but several authors have pointed out that the artery in the petrous canal may behave

differently than arteries elsewhere[38,88] and that there are histologic differences too.[18,65] These factors may be important in the localization of the arterial disease to this region. The condition described by Tolosa[108] was similarly located, but the granulomatous tissue was extra-arterial and occlusion of the vessel had not taken place; the third patient of List and Hodges[63] may have had a similar type of lesion.

Infrequent causes (3 per cent) include the case of Ehrmann,[34] in which the carotids were compressed by a large thyroid tumor, and that of Tölle[107] with the histologic changes of thromboangiitis obliterans.

MENTAL CHANGES

Valverdus (cited by Chevers[19]) described the effects of acute occlusion of the carotids on the mental state: "the carotid arteries being obstructed, or from any cause shut up, we immediately grow stupid and fall asleep." In chronic bilateral disease, 20 of the 69 patients (29 per cent) had mental changes; the psychiatric symptoms in two of the cases of Shimizu and Sano,[100] however, were not detailed.

There were severe mental disturbances in seven cases.[35,44,45] The patients of Fisher[44,45] were males with an average age of 73 years, and in each atheromatous lesions were responsible. The present case is the only example of bilateral involvement of the terminal portions of the internal carotid arteries by giant-cell arteritis, in which severe mental disturbances occurred. Furthermore, Vereker[113] and Migone and Mortara,[71] when discussing the psychiatric aspects of the disease, did not mention the carotid arteries. The pathologic process in case 1 of Eisenbrey and co-workers[35] is not known. In all but this case, the clinical picture developed over a period of five or six years and was one of progressive mental deterioration culminating in complete dementia in three. It did not appear to have any specific characteristics, nor was it invariably akin to the "frontal lobe syndrome" mentioned by Negrin,[76] but it closely simulated the state produced by diffuse cerebral arteriosclerosis of the elderly. Accompanying defects of language function (case 1 of Eisenbrey[35]) may make the picture more complex. In none of the seven patients would a diagnosis of presenile dementia have been seriously considered, except perhaps in that of Eisenbrey,[35] although Fisher[44,45] has popularized this possibility. Although the clinical diagnosis in the patient of Shimidzu[99] was Pick's disease, carotid occlusion was complete on only one side.

As the psychiatric manifestations of chronic bilateral carotid artery occlusion may at some stage of the illness be unaccompanied by signs of a focal cerebral lesion, confusion with a dementia of primary cerebral origin is possible. However, although this may take place in the elderly, a picture of mental dissolution occurring in the presenile period due to bilateral carotid disease and confused with presenile dementia seems less likely.

Less severe mental features, often intermittent, were present in the remaining 13 cases, but in most instances they have received only passing mention. There was "mental slowing" in the patients of Cooley and McNamara,[23] Oota,[78] Gilmour,[49] and Fisher,[45] and a memory defect in those of Raeder and Harbitz,[87] Aggeler, Lucia, and Thompson,[1] and Batley.[7] The patients of Takahashi[104] and Hultqvist[57] experienced hal-

lucinations, and "delirium due to cerebral ischemia" was present in those of Ehrmann[34] and Takahashi.[104] Two patients[22,35] had brief episodes of psychologic disorder, and Otto's[79] patient was depressed and languid. The pathologic findings in this group are shown in table 1.

There seems little doubt that mental changes may be present in some cases of bilateral carotid occlusion, although not as commonly as has been suggested. That they occur with unilateral obstruction is also established,[44] although care must be taken to avoid confusion with the manifestations of a dominant cerebral hemisphere disturbance when the carotid on that side is affected. As pointed out by Eisenbrey and co-workers,[35] the psychiatric changes occurring with bilateral occlusion do not differ from those with a unilateral lesion. They can also appear with partial closure of the lumina as the following case already mentioned by Samuel[95] illustrates.

Case 2. A housewife aged 91 was admitted on November 9, 1954, having fractured the right femur a few hours previously. An accurate history could not be obtained, but it appeared that she had been bedridden for at least three years, during which time evidence of mental disturbance had become apparent.

Examination. She was confused and disoriented and showed the usual features of senile dementia. The nervous system was normal, however. Peripheral vessels, including the carotid arteries, were not palpated.

X-rays of the right femur showed a subtrochanteric fracture of the shaft.

Progress. Her general condition deteriorated steadily, although her mental state varied from day to day. She never exhibited normal cerebration and she was usually noisy and uncooperative at night. She died on January 14, 1955.

Autopsy. The salient features were the fracture, severe generalized osteoporosis, osteoarthritis of the hips and knees, purulent bronchitis and bronchopneumonia, senile pyometra, arteriosclerotic kidneys with multiple cysts, and total alopecia.

The brain weighed 1,204 gm. and appeared normal externally. There was a noticeable lack of atheroma in the basal arteries; the circle of Willis was normal. In the right corpus striatum there were several small areas (2 mm. diameter) of cystic degeneration. Both internal carotid arteries had severe atheroma in the sinus portions with considerable reduction of the lumina but not sufficient to prevent the passage of some blood.

Comment. It seems probable that in this patient the mental deterioration was due mainly to the usual cerebral changes associated with senile dementia, but it is possible that the bilateral carotid constriction also played a part. In this respect it is interesting to note that, of 40 patients with pulseless disease,[24] 32 had complete bilateral occlusion and only five had mental changes, whereas in the remaining eight cases where obstruction was incomplete, four had these features. Moreover, Fisher[45] had a case of bilateral, severe narrowing with no clinical manifestations.

PRODUCTION OF MENTAL CHANGES

It has been assumed[44] that the clinical features of bilateral carotid occlusion are produced by chronic anoxia of cerebral tissue, but all the factors involved in this process are not yet known. Some may, however, be mentioned, as well as other possible etiologic agents.

Experimental Evidence for Cerebral Anoxia

Fisher[44,45] has suggested that the measured decrease of cerebral blood flow in patients with senile dementia[46,60] may at times be due to bilateral carotid occlusion. It is now suggested, however, although not accepted by all, that this occurs in aging persons without mental change.[39,98] In any case, there is no adequate correlation between men-

tal state and cerebral circulation.[40] Furthermore, when making direct measurements of the cerebral circulation in patients with cerebral arteriosclerosis by the method of Kety and Schmidt,[61] the same fall was recorded even though cases of carotid occlusion had been excluded clinically.[21] Finally, Ochs, Sensebach, and Madison[77] have found a normal cerebral blood flow in cases of unilateral carotid obstruction and, although a case with bilateral involvement has not been investigated, the diminution, if present, may not be as much as one would expect in view of this finding. However, the present method of measuring the cerebral blood flow[61] gives information concerning only the total circulation of the organ and local variations, if small, cannot be detected.

Collateral Circulation and Anomalies of the Circle of Willis

The most important factor in the production of neurologic and mental symptoms of carotid occlusion, either unilateral or bilateral, is the presence or absence of adequate anastomotic channels. If the carotid lesions are slowly progressive, the latter may open up[106,110] both by way of the external carotids through the ophthalmic arteries[12,36,89,93,105,111] and other branches[109] and the contralateral internal carotid through the circle of Willis. It is likely that collateral channels develop on and in the cerebral hemispheres,[33] but the amount of blood distributed from one part to another by this method is unknown. In cases where connections are adequate the clinical findings may be few, and the severity of the final outcome depends upon the degree of anastomosis achieved, although Houdart, Pecker, and Clay[56] have recently challenged this concept.

An obviously important consideration in this respect is the formation of the circle of Willis, and Bérard[9] was the first to point this out. Saphir[97] and Fetterman and Moran[42] related this factor to cerebral softening and hemorrhage. King and Langworthy[62] mentioned it with reference to carotid artery occlusion, as did Fisher,[43] and Askenasy and Wijsenbeek[2] found it of importance in their fourth case; Symonds[103] also has discussed the subject recently. In addition, our case illustrates the course of events when bilateral internal carotid artery obstruction takes place in the presence of anomalies of the circle of Willis, which are estimated by Morel and Wildi[75] to be present in some form in 77.2 per cent of all brains. The first part of the left anterior cerebral artery was small (figure 5) and represented a common anomaly of this vessel;[10,74] a defect of this vessel was also present in cases 2 and 3 of Miller[43] with unilateral occlusions. The majority of the blood to both frontal lobes, therefore, came from one internal carotid artery. The right posterior communicating artery was also rudimentary and could transmit no blood, a finding much the same as that reported by Askenasy, Wijsenbeek, and Herzberger[3] in a case of unilateral carotid thrombosis and by DeVriese.[27] Connections between the left and the right sides and between the carotid and the vertebral systems were grossly defective, as also occurred in the cases of Saphir[97] and Hindze and Fedotawa.[55] Before the onset of carotid disease, however, the blood supply of the brain was presumably adequate. As the flow of blood in the carotids decreased, a state of insufficiency developed, particularly in the territory of the anterior cerebral arteries, because an adequate

supply of additional blood from the various collaterals could not reach it. This explanation would account for the predominance of mental symptoms in our patient and also for the softening in the distribution of the right anterior cerebral artery, which produced the terminal signs. Had the congenital anomalies of the basal arteries been absent, it is possible that, like the patients of Gilmour[49] with comparable carotid disease, mental symptoms might have been less prominent.

Certain authors[10,27] have found a higher incidence of anomalies of the circle of Willis in mental patients, but they were rarely as severe as those in case 1 and carotid occlusion had not occurred. Furthermore, they may exist in otherwise normal individuals[54] in whom they are probably of little importance as isolated abnormalities. As far as patients with atheromatous lesions are concerned, Botton[13] found no significant correlation between cerebral arteriosclerosis and anomalies or asymmetries of the circle of Willis. Another factor concerning the basal vessels and the establishment of anastomoses is the extension of thrombus from the cervical portion of the internal carotid artery into its cerebral branches.[64] This, however, did not occur in case 1.

Fisher[44] has pointed out the frequency with which mental symptoms attend occlusion of the left carotid artery. Busch[16] has made a similar observation with other types of cerebral disease, although Maxwell[68] has recently refuted these conclusions on statistical grounds. It is, however, possible that some of the patients with carotid disease affecting the dominant cerebral hemisphere also had abnormalities of the basal vessels. In one case[83] there was an anomaly of the left common carotid artery, but the circle of Willis was not described. Furthermore, the role of language function disorder in these cases has not yet been adequately assessed.

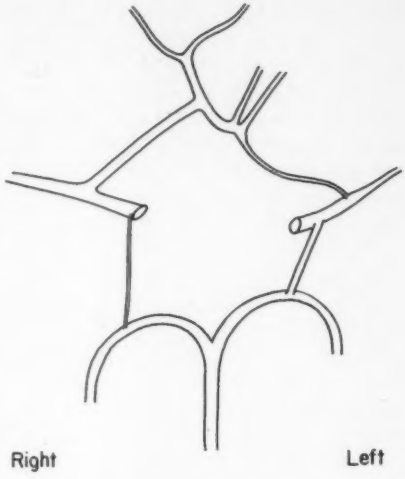


FIG. 5. Diagram of circle of Willis showing anomalous left anterior cerebral and right posterior communicating arteries.

Intracerebral Arterial Disease

It seems likely that in some cases of bilateral carotid disease the mental changes are due to the same pathologic process in the intracerebral arteries. In case 1 of Saphir[96] and in our second case atheroma produced the carotid lesions and probably the dementia also. Fisher,[44] however, noted the relative paucity of atheroma distal to the bilateral carotid block in his cases, as in ours, and this may be due to alteration in local blood pressure, which is known to influence atheroma formation.[114] A biochemical difference between the internal ca-

rotid and cerebral arteries is known to exist[14] and this may also play a part. In the cases of "pulseless disease" of syphilitic origin, it is possible that cerebral infection also occurred but there is no evidence for this to be found. In our patient giant-cell arteritis did not involve the intracranial branches of the internal carotids, although Vereker[113] has found it there in a patient with mental changes. Its occurrence with accompanying arteriosclerosis is also possible.[17]

Premorbid Personality

Finally another possible explanation of the mental changes is the well-known fact that the same or similar stimuli may produce a variety of mental changes in some individuals and none in others. The premorbid personality may, therefore, in part explain the degrees and types of psychiatric findings in the present series of cases. Thus our first patient had suffered a depressive illness several years before her death, presumably unrelated to the carotid lesions.

OTHER CLINICAL FEATURES

In addition to the mental changes, a variety of other neurologic abnormalities may be detected with bilateral carotid obstruction. Hemiplegia, paraplegia, and quadriplegia have been described, with accompanying sensory and visual deficiencies of varying severity. These features are frequently transient, and phenomena occurring on one side of the body and then on the other are characteristic. At an early stage, however, signs may be conspicuously absent and on this account a "functional" illness may be diagnosed.[35] The resultant clinical picture is dependent upon the efficiency of the collateral circulation and on the speed of onset of the arterial occlusions.

TREATMENT

Fisher[44] has speculated upon the possibility of operative measures in patients with bilateral internal carotid artery occlusion, and since then technics of vascular surgery have advanced. Anastomotic procedures have been described,[15,32] and others[84,85,90,102] have attempted thrombectomy and thromboendarterectomy of the carotid artery in their patients. Only one vessel was treated in these cases and the results to date, although not spectacular, are encouraging.

Early recognition is of primary importance and it is possible that by these and other means the brain will be spared the chronic anoxia and embolic episodes responsible for the clinical features of both bilateral and unilateral disease. A careful search for distal as well as proximal occlusion must be made in all appropriate cases, despite the fact that Fisher,[44] citing the experience of Hultqvist,[57] did not think it necessary. It is unfortunate that cases of bilateral occlusion, such as our case 1, exist because, although surgery is possible in the cervical portion of the artery, lesions of the terminal part present insurmountable obstacles at the present time. Moreover, correction of the anomalies affecting the basal arteries is likewise impossible. Thus knowledge of the condition of the whole vessel is obviously necessary before one part is operated upon, and information concerning the dynamics of the circle of Willis is of no less importance in view of our first case. Although anticoagulants have been used in carotid occlusion[41,43,72,73] and are claimed by some to be more effective than surgery,[25] they would be valueless in the absence of antemortem throm-

bosis, such as in case 1. However, the recent report by Harrison, Harrison, and Kopelman[53] indicates the value of the corticosteroids in the treatment of giant-cell arteritis. If the disease process in the carotid artery could be identified, its resolution with the re-establishment of blood flow might be possible.

SUMMARY

1. A case of obstruction of the internal carotid arteries in the cavernous sinuses due to giant-cell arteritis is described (case 1).

2. The principal clinical finding was progressive dementia and, of 69 collected cases with bilateral obstruction due to a variety of pathologic lesions, 20 had mental changes (29 per cent).

3. The latter are not characteristic and confusion with a presenile dementia did not arise. Partial, bilateral carotid occlusion may be found in patients with senile dementia (case 2) where its role, if any, is uncertain.

4. An important factor in the production of the clinical picture is the efficiency of anastomoses, and this may be interfered with by congenital anomalies of the circle of Willis (case 1).

5. Treatment of patients such as case 1 is impossible at the moment, although if the histologic diagnosis were known, corticosteroids would be eminently suitable. Vascular surgery may also modify the outcome in those with lesions more proximal in the carotid artery and thus early diagnosis is important.

The list of references documenting this paper is omitted here because of limitations of space, but will be included in the authors' reprints.

■ The influence of the nervous system on organic functions cannot be proved to be necessary by facts showing only that this system can act upon these functions. There is no question at all that the nervous centres and most of the nerves, directly or by a reflex action, can produce the greatest and the most varied effects on nutrition and secretions; but this power of acting of the nervous system does not and cannot show that these organic functions require for their normal existence a peculiar influence of the nervous organs. The only facts that can prove positively that a nervous influence is necessary to the organic functions, are to be found in the effects, of the absence of any influence of the nervous system.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Characteristics of Postural Tremor in Normal and in Various Abnormal States

Walter J. Friedlander, M.D.

POSTURAL OR STATIC TREMOR is the involuntary, rhythmic movement of a limb when that limb has assumed a particular posture. It is commonly tested for by having the individual hold his hands and arms extended at a 90-degree angle from the trunk. The presence of this tremor in otherwise normal persons was described at least as early as 1876[1] when Beaunis commented on the 10.5 per second rhythm of muscular contractions. However, it was Eshner in 1896[2] who definitely established the fact that postural tremor was a normal phenomenon; it was he who coined the term "tremograph." In spite of this early demonstration of postural tremor in normals, no mention of this normal phenomenon is made in most modern text books, the usual classifications of tremor, or the majority of scientific papers on tremor, and the reader is more often than not left with the impression that tremor in itself is an abnormal sign.

TECHNIC

Tremograms were obtained on a previously described apparatus.[3] A small, lightweight, alnico magnet was taped to the middle or index finger of each hand. The patient then rested his palms on a cross-bar, with his fingers gently extended so that they almost touched one of two coils on a second cross-bar parallel to the first. Hence the postural tremor of both hands was obtained synchronously.

The coils were connected to the input of a Grass model III electroencephalograph. Tremograms were obtained on all patients referred to the electroencephalography laboratory who had strength enough and were cooperative enough to hold their hands on this apparatus.

FINDINGS

Over 1,200 tremograms were obtained on about 700 patients. All of them had a definite measurable postural tremor. In this total group, 403 had at least a complete medical history and physical examination, and many of these also had special procedures, such as roentgenograms, electroencephalograms, spinal taps, air encephalograms, and so on. It is from this latter group that the following records were obtained.

Normals

From the group of 403 patients, 39 were selected as "normal controls." These met the following criteria: 1) no evi-

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dence of neurologic disease above the mid-dorsal spine, 2) normal electroencephalograms, 3) insufficient postural tremor to be worthy of comment when the patient was examined physically, 4) no physiologic evidence of anxiety nor a diagnosis of an anxiety neurosis, 5) no history of alcoholism, 6) no history of migraine or other diagnoses that may be associated with a tension state, and 7) no evidence of endocrine disease. It was felt that such a selection was better qualified as normal for purposes of control than the random selection of physicians, visitors to the laboratory, friends, and so on, who escape the scrutiny of a thorough history, complete physical examination, and electroencephalogram.

The tremograms were examined for the general type of frequency pattern (F.P.) and amplitude. The F.P. of the tremors varied from a regular eight to 12 second rhythm, which might be likened to "printed alpha" in the electroencephalogram, to a very fast, often poorly defined rhythm in which little or no eight to 12 per second components were seen. The fast frequencies were in the range of 15 to 24 per second. Small amounts of slow (three to seven per second) vibrations were seen in some tremograms, but in no record did this exceed 20 per cent of the total oscillations and perhaps even this could be considered a liberal estimate. An attempt was made to group these types of F.P. (figure 1):

A—An almost constant, regular, eight to 12 per second frequency with but very rare faster or slower frequencies.

AB—A group between A and B.

B—Easily identifiable eight to 12 per second frequencies, but sufficient faster beats to give the overall pattern a somewhat irregular and rapid appearance.

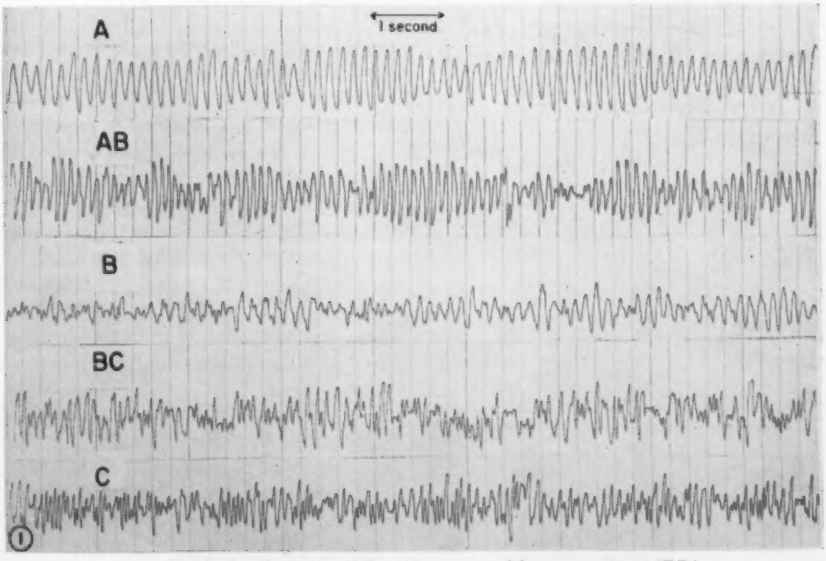

FIG. 1. Sample tracings of the various groups of frequency patterns (F.P.)

BC—A group between B and C.
C—Almost constant fast activity with very rare, random eight to 12 per second components.

Such a division of the tremograms gave a better picture of the over-all frequency characteristics than any classification according to the exact rates, since in most tremograms there was a continuous spectrum of frequencies which would make such a count an almost impossible task and would give such a variety of numbers that it would make comparison with other records extremely difficult. Vibrations of eight to 12 per second were chosen as the basic frequency band, because this was the one range of oscillations which was found in common in almost all records. The distribution of these F.P.'s in normals was as follows: A—two, AB—11, B—six, BC—13, and C—seven. When an attempt was made to group the records according to which of their eight to 12 per second frequencies were the most evident (regardless of the percentage of these frequencies), the distribution was: 12 per second—two, 11 per second—nine, 10 per second—15, nine per second—nine, and eight per second—two.

No correlation* was evident between the age of the patients (which ranged from 21 to 66 years) and either the F.P. (figure 2) or the dominant specific frequency in the eight to 12 per second band.

The measurement of the amplitude of the tremor was, unfortunately, not very exact. Minor differences in how far the magnet was from the coil could not be easily controlled. But probably more important was the fact that there was such a great variation of amplitude from one oscillation of the tremor to the next. Hence, calculations of the average amplitude could be done only by inspection and then rather arbitrary selection of an "average" tremor vibration. Keeping in mind that these amplitude meas-

*In this and subsequent statistical studies, if more than one tremogram was obtained, only the first one was used in any calculation, unless otherwise specified. This selection prevented one particular variable, such as age or type of F.P., which might be repeated in serial records of the same individual from weighing the statistics.

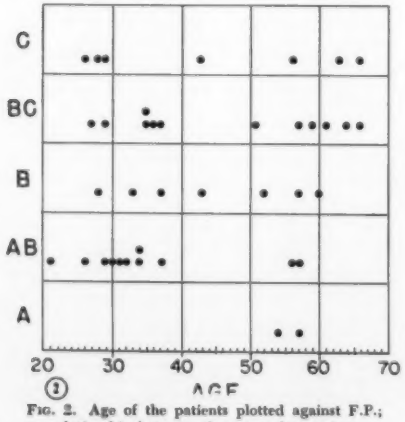

FIG. 2. Age of the patients plotted against F.P.; no relationship between these two factors is seen.

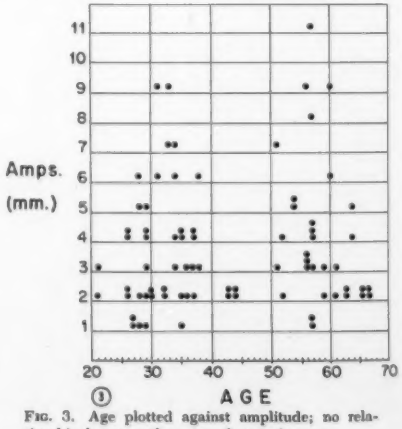

FIG. 3. Age plotted against amplitude; no relationship between these two factors is seen.

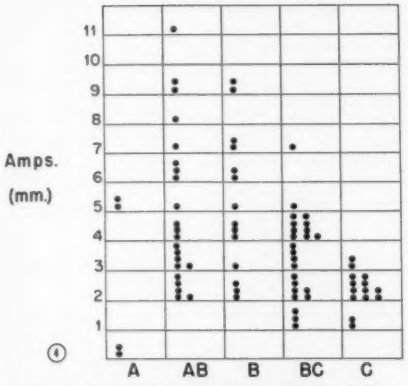

FIG. 4. F.P. plotted against the amplitude of the tremor; in the more regular, slower frequencies (AB) no relationship is seen, but in the faster frequency patterns (BC and C) there is a tendency to grouping in the lower amplitudes.

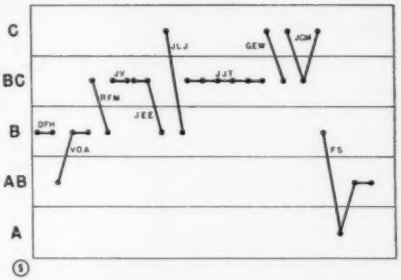

FIG. 5. Serial F.P.'s for each patient who had more than one tremogram; the greatest variations were not very marked and frequently the F.P. was constant from one record to the next.

urements were approximate, some interesting data became available. The amplitude in all records was measured during the first five seconds that the tremor was recorded and while the electroencephalograph's output was calibrated at 5 mm. per 50 microvolts. There was no relation between age and amplitude (figure 3). There was a suggestion of an inverse relationship between frequency of the individual vibration and its amplitude; however, in the over-all pattern of the record, though there was a suggestion of an inverse relationship of the amplitude and the fast F.P.'s (for example, BC and C), there was no relationship between the slower, more regular F.P.'s (AB) and amplitude (figure 4).

Thirty-five patients were right-handed. The approximate amplitude of the right hand tremor was compared to that of the left. The differences were not statistically significant ($P = < 0.001$). Ten patients had tremograms on two or more occasions. These were compared for variations in amplitude and F.P. Three had identical F.P. on more than one occasion, and the remaining seven were not greatly different on the several occasions (figure 5). As for amplitude, however, there was a considerable fluctuation from one record to the next (figure 6).

"Anxiety"

Twelve patients fitted the criteria of "anxiety," either having a diagnosis of anxiety neuroses or physiologic evidence of anxiety; in either case, the patients otherwise fitted into the previously described category of normal. The F.P. was not remarkably different than seen in the normal controls, although there was tendency for more fast records (BC and C) than in the control group. There was nothing in the pattern of the individual records per se to distinguish one condition from the other. However, the amplitude of the postural tremor in anxiety states was significantly greater than that seen in normals ($P = < 0.001$).

Chronic Alcoholism

Twenty-five patients had a diagnosis of chronic alcoholism; the criteria were rather indefinite but all of these patients admitted to heavy alcoholic consump-

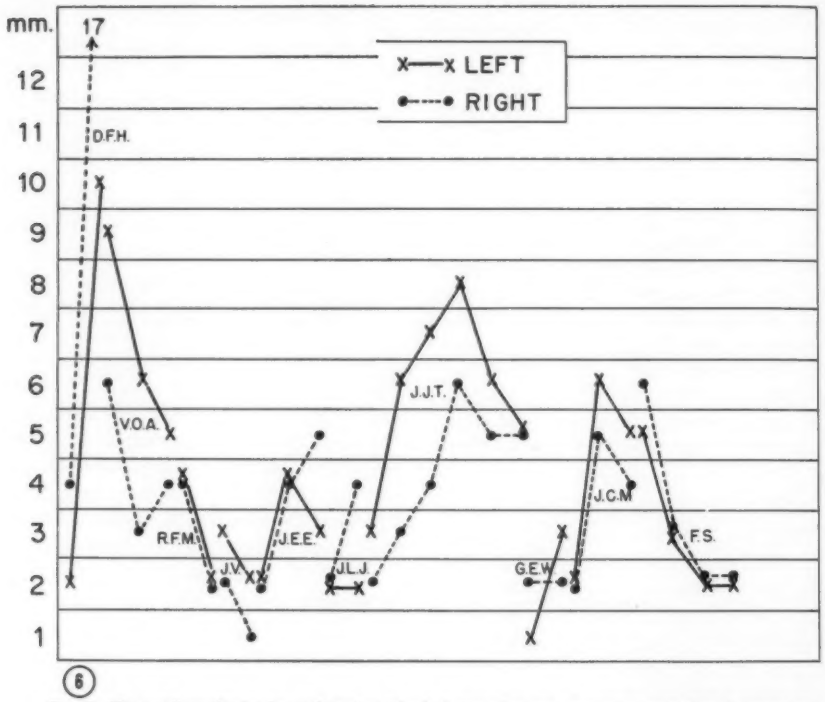

FIG. 6. The serial amplitudes for each patient who had more than one tremogram; variations between one time and the next are often considerable.

tion up until the time they were admitted to the hospital. None of these patients had clinical signs of unilateral motor or sensory deficit. Admission to the hospital was due to hepatic cirrhosis, polyneuritis, seizures secondary to alcoholism, cortical atrophy secondary to malnutrition and alcoholism, and delirium tremens. The total alcoholic group was divided into two parts: (group I) 12 patients in whom a postural tremor was noteworthy on examination, and (group II) 13 patients in whom no tremor was commented upon in the physical examination.

The F.P.'s resembled those of patients with "anxiety state" in that there tended to be fewer A and AB and more BC and C types than in the normal controls (figure 7). Also, in two of the patients there were larger amounts of tremor frequencies of less than eight per second than were seen in normals. In these two cases this variation occurred in patients who had a noteworthy tremor on physical examination; this slowing was unilateral and the predominant rate was about six per second.

The amplitude of the alcoholics' postural tremor, both in the group with obvious tremor and in the total group, was significantly greater than noted in the

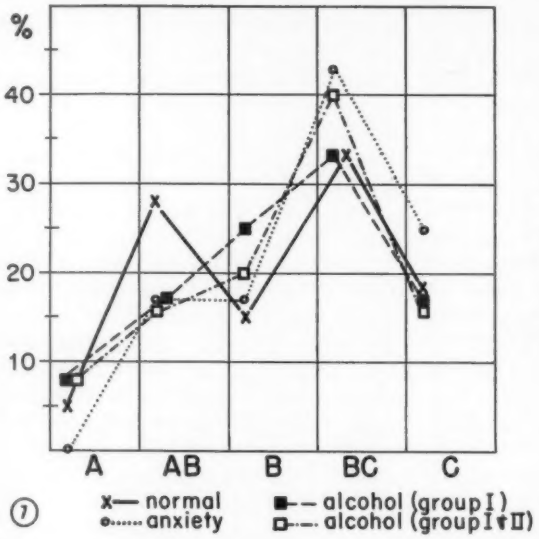

FIG. 7. Percentage of various F.P. types found in normals, anxiety states, chronic alcoholics with clinically remarkable tremor and the total chronic alcoholic group, that is, with and without clinically remarkable tremor; the distribution is about the same for all in the faster F.P. groups (BC and C), but there is a greater percentage of AB's in normals.

normal controls ($P = < 0.001$).

Parkinsonism

Twenty-eight patients had parkinsonism; 13 of these had paralysis agitans, nine had postencephalitic parkinsonism, and the remaining six did not have a definitely established etiology. All the patients had some degree of slow rest tremor which is characteristic of this illness. However, seven had a normal F.P. in their postural tremor; the remaining 21 had postural tremors whose frequencies varied between four and seven per second. The average amplitude of the tremor of all patients with parkinsonism was significantly greater than normal ($P = < 0.001$), regardless of whether they had a slow frequency or a normal F.P. type of postural tremor. The amplitude and frequency of patients with paralysis agitans were compared to those who had postencephalitic parkinsonism and in neither case was there a significant difference. Eight of the patients had more than one tremogram; usually there was no remarkable change between the individual records, although the slow frequencies often varied about one vibration per second; however, on rare occasions a normal F.P. was obtained which on subsequent records was replaced by the typical slow tremor rate.

Unilateral Central Nervous System Pathology

Seventy-seven patients had definite motor and/or sensory deficits due to central nervous system pathology predominantly on one side; 85 per cent of these patients had a bilaterally normal postural tremor. In those with an abnormal postural tremor, the affected limb might have had a higher, a lower, or an equal amplitude than the contralateral normal limb's tremor. The most prominent variant from normal was a disorder of F.P. with the presence of considerably slow and irregular vibrations (three to seven per second). The lack of a good corre-

lation between the side of the abnormal tremor and the side on which there was pathology makes tremography a poor clinical test, at least at this time.

DISCUSSION

Several characteristics of postural tremor that have been described here have been reported by others in the past: postural tremor is a universal phenomenon in normal individuals (table 1) and there is an inverse relationship between frequency and amplitude,[8,14,15] at least as far as the faster F.P.s are concerned.[11]

However, the only other available study that compared the relation between handedness and tremor was that of Eshner,[2] who gave the average rate of the right-hand tremor as 7.0 per second and the left-hand tremor as 6.7 per second; whether these rates were based on simultaneous recordings, whether this difference represented a significant one, or whether the individuals he tested were right-handed was not stated. I could find no significant difference between hands, either in amplitude or frequency pattern. Another factor in postural tremor which has been rarely touched upon is the role of age. Graham[11] felt that there was no relationship between age, sex, rate, or amplitude; substantiation for this has been found here. This particular lack of correlation would suggest that senile tremor may not be simply a variant of normal postural tremor.

The factor which varied between normals and anxiety states or chronic alcoholism was the amplitude and not the frequency. In other studies it has also been shown that the usual variable factor in different conditions is amplitude rather than rate. Graham compared the rate and amplitude of postural tremor in anxiety states and normals and found no statistically significant differences in the rate, but there was a statistically significant difference in amplitude. Tuttle and co-workers[16] found that "magnitude" (amplitude?) of tremor varied directly with the intensity of exercise but that the rate of the tremor was unaffected. Administration of adrenalin has been reported[17] to increase amplitude, but had little or no effect upon frequency. Emotional stimuli[18] modify the amplitude

TABLE 1

HISTORICAL REVIEW OF REPORTED FREQUENCIES OF NORMAL POSTURAL TREMOR

Author	*Year*	*Rate (per second)*
Beaunis[1]	1876	10.5
Wolfender[4]	1888	5.1
Peierson[5]	1889	10
Dana[6]	1892	10–12; usually 10
Eshner[2]	1897	6.7
Mehrtens[7]	1928	9–15
Sollenberger[8]	1937	5–15
Jasper[9]	1938	8–13
Lazarus[10]	1943	7.03 1.57
Graham[11]	1945	13.4
Campbell[12]	1947	9–16
Silverman[13]	1948	7–21

more than the rate. The tremor of hyperthyroidism has been reported[10] to differ from that of normals mainly in amplitude and only minimally in rate. In this series, the F.P. showed only minor changes when normals were compared to anxiety states or chronic alcoholism, but between the same groups there was a statistically significant difference in amplitude. However, tremor rate can alter significantly under certain circumstances. In parkinsonism both amplitude and rate are significantly different from that seen in normals. In patients with hemiparesis or hemihypesthesia there may be a significant slowing of the tremor rate. Too, there may be some difference in the type of oscillation; the pattern of the vibration in parkinsonism is regular, in contrast to the irregular form of the beat seen in some patients with focal central nervous system disease.

Perhaps as this study continues, certain criteria may become evident enough to increase the clinical usefulness of this technic. Actually we are not much further along than Peierson[5] was in 1889 when he wrote: "While there may not be significant data . . . . to arouse any great hopefulness of a diagnostic value of this means of examination, still considerable light may be thrown upon the nature of tremors in general . . . ."

SUMMARY AND CONCLUSIONS

1. One hundred per cent of all persons examined, who had strength enough and were cooperative enough to hold their hands and arms extended, had a measurable postural tremor.

2. The characteristics of the normal postural tremogram have been stated. There appears to be no correlation between age and frequency or age and amplitude. There is a suggestion that the faster frequency patterns (F.P.) have a lower amplitude. There is some degree of constancy in the F.P., but not in the amplitude of the tremor of the same individual from one examination to the next.

3. The tremor of anxiety differs significantly from normal postural tremor in amplitude only.

4. For the most part, the postural tremor of the chronic alcoholic is not distinctive from the tremor of anxiety. A few alcoholics, however, show different characteristics than either normal or anxiety states in that they had a greater amount of slow vibrations (seven per second or less).

5. Some patients with parkinsonism have a postural tremor indistinguishable in type from normal except for a greater amplitude. There is no statistically significant difference between the rate of postural tremor or amplitude in postencephalitic parkinsonism or paralysis agitans.

6. Patients with unilateral central nervous system disease usually have a normal postural tremor. The most striking deviation from normal is an alteration of rate, with the presence of slow and irregular vibrations.

7. Tremography, at least at this time, has not proved to be of much value in clinical diagnosis.

The author wishes to thank Jerome Fisher, Ph.D. for his assistance in the various statistical analyses.

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■ It is very important, on account of the treatment, to find out if there is an unfelt aura, and what is its starting point. In consequence of this view, the condition of all the organs of the body ought to be carefully inquired into.

If the unfelt aura starts from some parts of the skin, or from some organ not deep-seated, as the testicle, or some part of mucous membranes, near the skin, either the first contractions in a fit, or the most violent or the most prolonged, are found in the neighborhood of the point of starting of the aura. If no indication of this kind can be furnished by the persons who have seen the fits, it will be well to try the application of a very powerful galvanic current, with dry conductors, on the various parts of the skin, when the patient expects to have a fit. I have, in this way, twice ascertained the point of starting of an unfelt aura; a fit has been produced by the galvanization of certain parts of the skin. Of course there are many cases where such a means of diagnosis ought not to be employed; every one will understand what are those cases.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System,* published in 1860.

Cysticercosis of the Nervous System

Diagnosis by Means of the Spinal Fluid Complement Fixation Test

Dionisio Nieto, M.D.

IT IS GENERALLY AGREED that cysticercosis in man is exclusively due to the development of *Taenia solium* larvae, called *Cysticercus cellulosae,* which is a frequent parasite in the pig. The *Cysticercus bovis,* larva of *Taenia saginata,* grows in the cow. It apparently does not affect man, although some cases have been reported. Arndt, Bitot, and Sabrazes pointed out its presence in the brain and Volkers in the eye.[1] According to Mosler and Peiper[2] these data are unreliable, since these could have been cases of degenerated *Cysticercus cellulosae.* Other cases have been reported, namely: *C. tenuicollis,* larva of *Taenia hydatigena* of the dog; *C. fasciolaris,* larva of *Taenia taeniaeformis* of the cat; and *C. pisiformis,* larva of *Taenia pisiformis* of the dog. Yet according to Neveu-Lamaire,[3] these observations are very doubtful and cannot be entirely accepted.

There are two other *Taenias* whose larvaeceous forms can be found in man and eventually in the nervous system: the larvae of *Taenia echinococcus* of the dog, called hydatid, which forms hydatid cysts and localizes in different viscera (liver, lung, brain), and the *Taenia caenurus* or *Taenia multiceps,* also of the dog, whose larva, *Caenurus cerebralis,* is habitually found in sheep's brain. Marie and Foix found it once in the human brain and this case was studied by Brumpt.

In man, *C. cellulosae* represents the most frequent cerebral parasite and presents the most varied neurologic and psychiatric syndromes. It occurs more frequently than is generally assumed, and many times it is not identified because of difficulties in establishing a diagnosis. These difficulties have been solved by doing a spinal fluid complement fixation test. The application of this diagnostic procedure has enabled us to collect 168 cases, which constitute the material of the present study.

HISTORY

The first descriptions of cysticercosis are presumably that of Paranoli, who in 1550 found some vesicles filled with liquid in the corpus callosum, in a man dead of an ictus, and that of Rumler,

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who in 1558 published the case of an epileptic in whom he found vesicles in the dura. Yet, these authors did not identify the nature of such vesicles. Leuckart and Küchenmeister[4] were the first to identify these formations as *C. cellulosae*. In 1860 Virchow[5] described meningeal racemose cysticercosis of the base of the brain without identifying its nature. Virchow's description was later interpreted by Zenker.[6] In 1862 the great German psychiatrist, Griesinger,[7] published an article on "*Cysticercus* and their diagnosis," in which he rightly analyzed the convulsive syndromes caused by this parasite. In one case the diagnosis was made during life. In 1867 Lombroso[8] published the case of an epileptic in whom he found *Cysticercus*. In 1874 Heller[9] described "*Cysticercus* meningitis," and in 1890 Askanazy[10] reported a case of endarteritis obliterans due to *Cysticercus* meningitis of the base of the brain.

By the turn of the century, reports of isolated cases of nervous cysticercosis had multiplied. Volovatz[11] cited 414 cases of cysticercosis limited to a single organ, of which 149 were related to the nervous system. In Vosgien's monograph,[4] cysticercosis is reviewed in all its localizations in man, as well as in the dog, sheep, and roe deer; 807 human cases are summarized, 330 of which had nervous system localization. Vosgien spoke of interest in the complement fixation test for diagnosis. In 1912 Henneberg[1] described the clinical and anatomopathologic features, but made no mention of the diagnostic possibilities. Weinberg in 1909 tried the complement fixation for the first time, testing the serum of infested swine, and in 1910 Robin and Fiessinger[12] attempted the test in man with doubtful results. Moses[13] in 1911 used an aqueous extract of *Cysticercus* as antigen for the reaction in serum of three patients with cutaneous cysticercosis and in the spinal fluid of a patient with cysticercosis of the brain. Grund[14] in 1913 pointed out eosinophilia of the spinal fluid. In Guccione's monograph[15] published in 1919, he emphasized the eosinophilia in certain cases and also the positive results of the complement fixation test in the serum of patients with cutaneous or cerebral cysticercosis. Schenk[16] diagnosed a living case of cysticercosis by the spinal fluid eosinophilia. Rizzo[17,18] insisted on the diagnostic importance of spinal fluid eosinophilia. The Brazilian authors, Pessoa and Silveira,[19] utilized the spinal fluid complement fixation test with good results. Rothfeld[20] did a precipitation test. Lange[21] reported good diagnostic results with the spinal fluid complement fixation test in 24 cases of nervous system cysticercosis.

Cases of nervous system cysticercosis are so numerous that it is not possible to refer to them in detail. However, it is important to summarize the most frequent symptoms, together with fundamental aspects of the pathologic anatomy, and to emphasize the certainty with which a diagnosis can be established by spinal fluid examination in the majority of the cases.

SYMPTOMATOLOGY

Henneberg[1] classified nervous system cysticercosis into nine groups: 1) asymptomatic cysticercosis incidentally found at autopsy, 2) cases in which there are neurologic and psychiatric symptoms which cannot be positively attributed to the presence of *Cysticercus*, 3) essential epilepsy, 4) focal epilepsy, 5) cases in which *Cysticercus* determines a symp-

tom or focal syndrome of any type, 6) predominant psychic changes, 7) *Cysticercus* basal meningitis, 8) ventricular cysticercosis, and 9) spinal cysticercosis and *Cysticercus* spinal meningitis.

The presence of *Cysticercus* in the brain which does not produce symptoms is undeniable. Not only are there cases in which one, two, or three *Cysticercus* are located in silent cerebral zones, but on occasion several parasites are found without the patient ever having any clear neurologic or psychiatric symptoms. In one case we have found a *Cysticercus* localized in the lenticular nucleus which had not produced special symptoms. That is why Henneberg wisely established that second group in which, in spite of finding *Cysticercus*, there cannot be a diagnosis of certainty in relation to symptomatology. From a general point of view, these facts would cause the same problems already known in relation to asymptomatic neurosyphilis and other similar processes. They cannot be interpreted in the sense that the cerebral tissue tolerates the presence of these parasitic forms without endangering its functions.

Since it is impossible to refer in detail to each of the 168 clinical cases which constitute the material of this article, we shall limit ourselves to the most frequent syndromes observed.

The epileptic symptoms are undoubtedly the most frequent. It has been generally admitted that cysticercosis causes epilepsy of the focal type. Yet in our material the nonfocal type of epilepsy was more frequent. That is why the lack of localized manifestations does not constitute an argument against the possibility of cysticercosis. Many patients diagnosed by means of the spinal fluid complement fixation test were hospitalized with a diagnosis of essential epilepsy. However, many cases which had several neurologic and psychiatric symptoms had epileptic seizures from the beginning or during the course of the disease, which later disappeared and did not constitute the main clinical manifestation.

In second place, there are many cases in which symptoms can be attributed to the basal *Cysticercus* meningitis. Here we found mainly two syndromes: intracranial hypertension and a psychiatric picture of the organic syndrome type. Intracranial hypertension with papilledema and all of the intracranial manifestations of tumors occurs frequently in cysticercosis and can only be differentiated from true tumors by spinal fluid examination. In many cases there are radiologic signs which indicate hyppophyseal tumor because of alterations in the sella turcica. The intracranial hypertension symptoms are produced by obstruction of the Magendie and Lushka foramina and by inflammatory invasion of the structures which form the roof of the fourth ventricle. In other instances the basal meningitis partially respects these structures, and instead predominates in the chiasmatic cistern in the floor of the third ventricle. If so, the symptomatology is fundamentally psychic with dementia-like manifestations very much like those observed in general paresis, with which it is frequently confused. Even the spinal fluid data, which indicate a chronic inflammatory lesion with negative Wassermann reaction, can give positive reactions with the precipitation test, such as Kahn's and Mazzini's and others. This basal meningitis frequently produces optical neuritis which often ends in blindness.

Cysticercus are found also in the cere-

bral ventricles. Only when localized in the fourth ventricle can they be an indication of this symptomatology. Bruns described the syndrome which bears his name and which mainly consists of intense and periodic headaches, vertigo-like crises which appear rapidly and disappear in a few days or weeks, and central type vomitus. The most characteristic feature of Bruns' syndrome is the headache and vertigo which can be brought about by rapid movements of the head. It has been thought that this would be conditioned by displacement of the vesicle. Yet Henneberg did not accept this pathogenesis and believed that the sudden appearance of symptoms by head movements could be due to the dilated fourth ventricle, which would push the anterior medullary velum upward and cephalad, thus pressing on the great cerebral vein of Galen. Fuentes[22] described a case of cysticercosis in the fourth ventricle in which there were diencephalic and bulbar symptoms, and explained their association as paroxysmal obstruction of Magendie's foramen. However, since it was necessary to suppose that both of Luschka's foramina were obstructed at the same time, a momentary interruption of the passage of fluid to the subarachnoid spaces is not tenable with a paroxystic syndrome. It is our understanding that Henneberg's interpretation explains best the several symptoms which can be observed in this location. In our material we have a case which was diagnosed as simple dementia with some atherosclerotic signs. There was no symptom to indicate a fourth ventricle location. On autopsy we found two *Cysticercus* occupying the fourth ventricle cavity, which had not produced any symptomatology. We have diagnosed another case of fourth ventricle location by the spinal fluid examination which showed a typical Bruns's syndrome.

In many instances the symptomatology is purely psychic. There can be states of mental confusion of variable duration.

The clinical manifestations of nervous system cysticercosis can be extraordinarily variable. Those interested in this aspect may consult Henneberg's chapter[1] or Lopez Albo's monograph.[23] This variability is explained by the peculiarities which the parasite's pathology offers in the nervous system.

PATHOLOGY

We do not know the morphologic evolution of the lesions from the moment at which the *Taenia* embryo localizes in the tissue until it is transformed into a *Cysticercus*. It is known that the most frequent mechanism of infestation in man consists of fresh vegetable ingestion (especially lettuce, cabbage, and strawberries) contaminated with *Taenia* larvae, although autoinfestation of *Taenia* carriers is also possible. On arriving in the stomach, the eggs lose their coat by action of gastric juice, thus freeing the embryo. This, in turn, actively pierces the stomach or intestinal mucosa, penetrates into the capillaries, and spreads through the circulation until it fixes itself to any tissue, for which it has to cross the capillary wall again. Although this location must be a matter of chance, experience shows that there is a marked predilection for striated muscle and nervous tissue. It is possible that the embryo reaches other tissues with the same ease, but may not find the ideal conditions for its development. It might be thought that glycogen is necessary for the transformation into

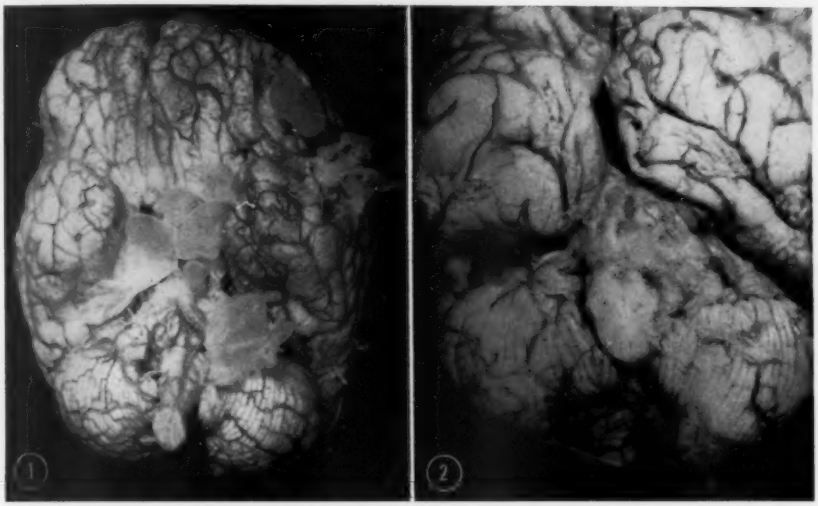

FIG. 1. Racemose meningitis of the base of the brain.

FIG. 2. Chronic basal meningitis not showing grossly recognizable *Cysticercus* vesicles, but marked thickening of the pia-arachnoid.

Cysticercus, but the fact that they are rarely found in the liver destroys this possibility. It is generally thought that the *Taenia* embryo, once fixed in the tissue, changes into a *Cysticercus* in approximately two months.

The lesions produced are variable and depend fundamentally on three factors: number of parasites, location, and evolution time. The number can vary from one to over a hundred. The location can be meningeal, parenquimatous, or ventricular, the first being the most frequent. In many cases the three forms are combined. In the meningeal location, the *Cysticercus* are found adhering mainly to the pia and lodged in the subarachnoid spaces in which they float freely. Others are found fixed under the pia and burrowed in the cortex. With greater frequency the meningeal *Cysticercus* are localized at the base, growing in the several subarachnoid cisterns (cisterna magna, cisterna pontis, cisterna superior, cisterna interpeduncularis, and cisterna chiasmatica). In the cisterns the vesicles may grow in very large cluster forms which extend in all directions, constituting the so-called racemose meningitis of the base of the brain described by Virchow in 1860. In figure 1 we reproduce a photograph of a cerebrum showing the typical aspect of this variety. The chiasmatic and interpeduncularis cisterns are filled with large vesicles extending into the left Sylvian fissure. In the left cerebellopontine angle another great cluster of vesicles is found. With the time, these vesicles shrink and their membranes with the scolex become covered by inflammatory tissue, which infiltrates the pia-arachnoid and even the dura. The process of chronic proliferative inflammation extends to all the basal

surface of the brain and the cisterns magna and superior, without macroscopically identifiable vesicles. In cases of many years evolution, one only observes an inflammatory thickening of the pia-arachnoid from the chiasmatic region to the medulla and cerebellum, without traces of vesicles in sight. Figure 2 is a photograph of the base of a brain with basal meningitis whose *Cysticercus* could not be identified macroscopically. It belonged to a patient whose illness lasted over ten years. It is important to remember this because the nature of the process can be missed entirely at autopsy or at a surgical procedure.

Microscopically the lesions show a structure that can vary according to age. If we consider an elemental lesion which is produced in the tissue where the *Cysticercus* is implanted, the alterations observed are the following: Around the vesicle's membrane there is a band of inflammatory infiltration constituted by plasma cells, lymphocytes, eosinophils, large mononuclear cells, and some giant cells of the foreign body type. There is marked proliferation of precollagen and collagen fibers. The collagen growth is particularly abundant in the peripheral zone, forming a sort of capsule which encloses the parasite. In the vessels, besides the adventitia infiltrations, a more or less marked endarteritis is observed, very like the one found in vascular syphilis (figure 3). These inflammatory alterations are usually limited to the close neighborhood of the parasite and disappear a short distance from it. When the *Cysticercus* has been implanted a long time, it calcifies and this process can be seen at different stages. At times it is the site of caseous disintegration. In cases of long evolution, the inflammatory barrier is less rich in cellular elements, the eosinophils disappear, and collagen fibers are abundant. The characteristic structure of *Cysticercus cellulosae*, the scolex's hook crown, can only be recognized histologically if the parasite has not disintegrated and if the section contains it. Generally it is not seen unless serial sections are made. For identification of the *Cysticercus*, it is best to extract the scolex from the vesicle's interior, press it between two slides, and observe it under the microscope. In this way the hook crown is always found if it has not disintegrated.

When the *Cysticercus* has burrowed into the cerebral cortex, the inflammatory reaction is usually more circum-

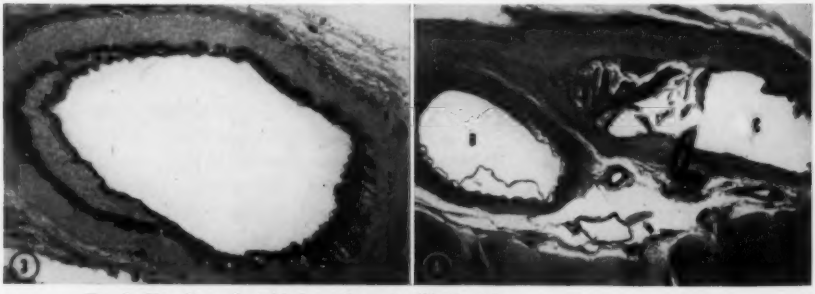

FIG. 3. Vascular endarteritis in cysticercosis. Elastic stain.

FIG. 4. Basilar artery (*B*) and a degenerated *Cysticercus* (*C*) at the level of the pons.

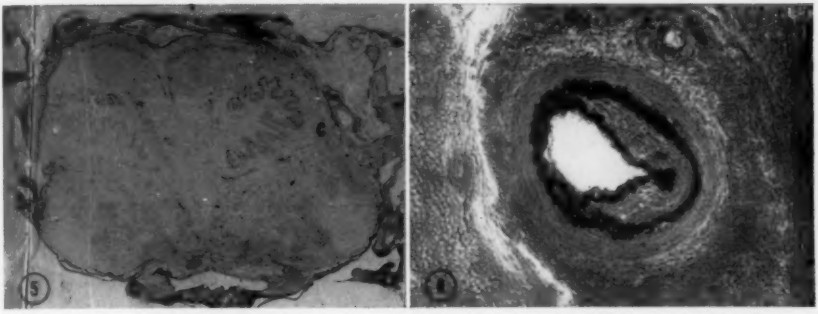

FIG. 5. Section through the middle third of the medulla. *C* points to the posteroinferior cerebellar artery surrounded by irregular cavities, rests of degenerated *Cysticerci*, and thickening of the pia-arachnoid. Nissl stain.

FIG. 6. Higher magnification of one of the arterioles involved in the inflammatory tissue shown in figure 5. Notice severe narrowing of the lumen. Elastic stain.

scribed due to the lack of connective elements, but it offers the same features.

The lesions show peculiar features when the *Cysticercus* is localized in the base. In those cases in which the parasites retain their vesicles and cluster-like forms, the inflammatory process has the same morphologic features described above, but the reaction is more extentive and a more diffused basal meningitis is produced. The cellular elements of the inflammatory tissue are lymphocytes, plasma cells, polynuclear neutrophils and eosinophils (if the process is not very old), large mononuclear cells, and some giant cells. All these elements are enclosed in a dense net of precollagen and collagen fibers. The arteries present a marked adventitial infiltration with intimal proliferation, and sometimes a true panarteritis. When the process is of several years' duration, the *Cysticercus* vesicles, after undergoing a retraction, are enclosed in the inflammatory proliferation, the scolex degenerates, and they are only partially infiltrated with calcium salts. The rest of the vesicle can hardly be identified, even microscopically. In figure 4 we reproduce a photograph of the anterior side of the pons which includes the basilar artery (*B*) and a cavity of its side (*C*) of difficult interpretation at first sight, but in reality it is a degenerated *Cysticercus* vesicle enclosed in a thick inflammatory tissue. Inside only very altered traces of the scolex could be recognized.

Figure 5 is a photograph of a bulbar section. In one of its lateral sides, precisely at the level of the inferior olive, a deformed mass can be seen with several cavities, which are the remains of one or two degenerated *Cysticercus* vesicles. The vertebral artery is anterior (*V*) and the posteroinferior cerebellar artery (*C*) is the one surrounded by inflammatory tissue, with great hyperplasia of precollagen and collagen fibers. The arteries show endarteritis changes (figure 6). This patient did not show the posteroinferior cerebellar artery thrombotic syndrome, however.

In cysticercosis of the base of the brain, it is common for the inflammatory process to extend to the roof of the fourth ventricle. In figure 7 we repro-

duce a photograph of a fourth ventricle section in its inferior half, in which the great inflammatory thickening of the tela chorioidea and of the plexus is observed. In figure 8, with greater magnification, the dense inflammatory infiltration of these structures is seen. In this way it is explained that Magendie's and Luschke's foramina, from where the fluid passes to the subarachnoid spaces, becomes obstructed more or less completely and causes the development of internal hydrocephalus, which in turn explains the intracranial hypertension.

The great variety of lesions which cysticercosis can produce makes a detailed description of all the pathologic manifestations impossible. It is thus understandable that the clinical manifestations may represent a variety of syndromes. The number of parasites, their location, and the intensity and extent of the inflammatory reaction constitute the fundamental factors in integration of the pathologic and clinical picture.

DIAGNOSIS

Since nervous system cysticercosis can produce the most varied of neurologic and psychiatric syndromes, the diagnosis cannot be made clinically. Subcutaneous nodules identified by biopsy as *Cysticercus* can suggest the diagnosis. Yet the coincidence of nervous as well as cutaneous localization is exceptional. Among the 168 cases which constitute our material, only three had evident cutaneous *Cysticercus*. The same can be said of the opaque nodules which correspond to calcified *Cysticercus,* and which sometimes are visible in skull films. In the first place, they must be calcified to be visible, and this only occurs after a long period of evolution; in second place, we have observed several cases which at autopsy had wholly calcified nodules in the brain which had not been visualized in several radiographic studies. On the other hand, since these images are not specific but only suggestive, their diagnostic value is very poor.

There is no characteristic hematic change. Only when there are subcutaneous *Cysticercus* can there be some eosinophilia.

There are certain alterations in the spinal fluid which permit a positive diagnosis. Practically all cases of nervous system cysticercosis show inflammatory changes in the spinal fluid, consisting of

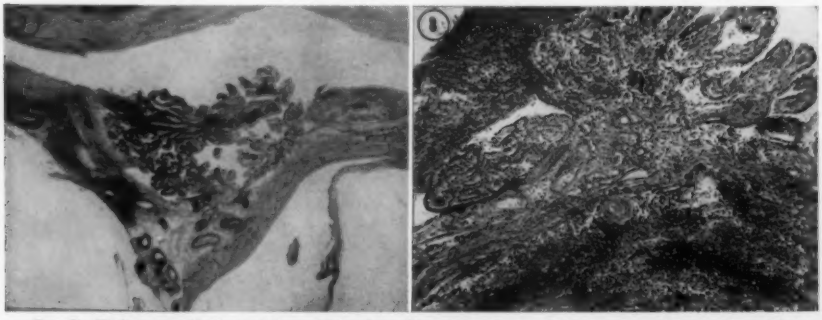

FIG. 7. Higher magnification of figure 5 to show the inferior angle of the fourth ventricle with marked inflammatory thickening of the tela choroidea, the plexuses, and the ependyma. Nissl stain.

FIG. 8. Detail of figure 7 through the choroid plexuses showing the diffuse cellular exudate. Nissl stain.

increase in the total number of cells with some eosinophilia, increase in the total protein, positive reaction for globulins, and a decrease in sugar content, with a negative Wassermann reaction.

The increase in the number of cells oscillates between very wide limits. The majority of our cases show a pleocytosis with figures between 10 and 100 elements. In 24 cases the number of cells was above 100 elements. In 52 cases this figure was below 10. We have seen a case in which the spinal fluid had 953 cells per cubic mm. and was cloudy. Yet the patient had no fever or clinical signs of meningitis. This is absolutely exceptional. The predominant cellular elements are lymphocytes. Polynuclear neutrophils are present in a proportion which oscillates between 1 and 5 per cent. The presence of eosinophils is almost constant. The majority of cases presented an eosinophilia between 1 and 6 per cent. In 24 of our cases no eosinophils were found. Two cases showed 35 per cent for one and 40 per cent for the other.

The presence of eosinophilia in the spinal fluid, although it is suggestive for the diagnosis, is not pathognomonic. We have verified a 12 per cent incidence of eosinophilia in the spinal fluid in a case of lumbar myelitis due to antirabies vaccination. In one case of tuberculous meningitis we found an eosinophilia of 38 per cent. In one case of onchocercosis we found a 5 per cent eosinophilia. It is known that cases of neurosyphilis can also show eosinophilia in the fluid.

The total protein is moderately increased in the majority of cases, oscillating between 50 and 100 mg. per 100 cc. In 25 cases this figure was higher than 100 mg. The globulin reactions (Pandy, Weichbrodt) are positive, and their intensity runs parallel with the total protein figure.

The glucose was between 20 and 50 mg. in 96 cases. In ten cases this figure was below 20 mg. In 46 cases it was above 50 mg. In one case we have found a figure as low as 5 mg.

The Wassermann reaction is constantly negative. In some cases a delay in hemolysis was observed in the tube which contains the largest quantity of fluid. The Kahn and Mazzini tests produce frequent weak positive reactions and even some of greater intensity. Because of this a great number of cases of nervous system cysticercosis are erroneously interpreted as neurosyphilis.

The spinal fluid examination in nervous system cysticercosis which shows inflammatory changes, with eosinophilia and decrease in glucose, can make suspect the process. Yet, this is not sufficient to establish a diagnosis.

In view of this situation, we started in 1942 a series of investigations directed to solve the diagnostic problem by means of the spinal fluid complement fixation test. The antigen was prepared in the following manner:

We collected from the slaughterhouse some 15 kg. of pig's meat highly infested with *Cysticercus cellulosae*. From among the muscle fibers the vesicles were extracted one by one and put into Petri dishes with physiologic saline solution. Several thousand were thus collected. The particles of connective tissue or the connective capsule in which many were enclosed were carefully removed from each vesicle. Once completely cleaned, they were washed five or six times with normal saline solution. After this, they were washed with pure acetone. Later they were put into several Petri dishes in one single layer and were placed in

an oven at 37° C. for drying. In the course of four hours, the drying process is complete. This dried material is put into a mortar and submitted to trituration until it is reduced to the finest powder. This powder is then treated by extraction with absolute ethyl alcohol in a proportion of 100 cc. of alcohol to each 10 gm. of powder. Extraction was maintained for ten days and the container shaken once in a while. It was later filtered through a double filter paper.

This alcoholic extract of *Cysticercus* was employed as antigen for the complement fixation test. The technic was exactly the same as that used for the Wassermann reaction, only with a different antigen. The first titration essays were done with blood serum from an intensely infested pig. It turned out that the pig's blood serum gave a positive reaction with a 0.5 cc. of the 1/140 dilution. With this same dose a series of blood serums from apparently normal persons was negative. The antigen was tested with a series of 40 spinal fluids which did not show any cytochemical change, and the reaction was completely negative. Thus with this dose, there was no anticomplementary action. Later it was tested with spinal fluids of patients suspected of cerebral cysticercosis. These fluids showed pleocytosis, eosinophilia, and decreased glucose, with a negative Wassermann reaction. The complement fixation test with the *Cysticercus* antigen was positive with 0.2 cc. of fluid. In these two patients the diagnosis was proved at autopsy. In successive preparations of the antigen, we have done the titration only with spinal fluids from patients in the psychiatric hospital.

For performance of the complement fixation reaction in the spinal fluid we prefer to follow the classical technic of Hauptmann, without the modifications which have been used in recent years to increase its sensitivity. We maintain this criterion for several reasons. If the sensitivity is increased in the Wassermann reaction, then its specificity can decrease. With very sensitive technics, the spinal fluid in cysticercosis can give slight or moderate positives, which are completely unspecific. If it is kept in mind also that the antigen used in the Wassermann reaction is not really specific, and that the inflammatory process which accompanies cysticercosis is quite similar to that of syphilis, it may be understood that forcing the sensitivity of the technic can only result in false positive results. For the same reason, it has always been advised not to utilize flocculation tests such as Kahn, Meinicke, and Mazzini in the spinal fluid.

By means of the spinal fluid complement fixation test with *Cysticercus* antigen such as we have described, we have identified 168 cases of nervous system cysticercosis in the last 12 years. The verification of the *Cysticercus* nature of the process has been proved in 18 cases at autopsy and in 40 cases at operation. In the remaining cases there has been no operative proof or autopsy, yet the clinical picture and evolution of the illness in these cases are compatible with such a diagnosis and not explainable in any other way, especially the changes in the spinal fluid.

On the other hand, the reaction has been constantly negative in the following processes: meningococcic meningitis, pneumococcic meningitis, tuberculous meningitis, polyneuritis with albumin-cytologic dissociation, multiple sclerosis, brain abscess, brain tumor, and the most varied cases of vascular diseases of

the brain.

Of special importance is the behavior of the complement fixation test with *Cysticercus* antigen in the neurosyphilitic fluids. About 30 per cent of fluids with a positive Wassermann reaction are positive also to a test for cysticercosis. This fact could make one think that the test has no specificity. Yet, if we remember that every spinal fluid with inflammatory changes and positive Wassermann test should be forcibly considered as neurosyphilis, investigation of the *Cysticercus* reaction is superfluous. There would remain the theoretical possibility that 30 per cent of neurosyphilitic fluids, in which the complement fixation test for cysticercosis is also positive, could be interpreted as an association of the two processes. We have not been able to investigate this phase to date. Yet, in principle, we do not suppose it is so and believe we are dealing with false positive.

Thus, the negative Wassermann spinal fluids that are positive to the complement fixation test for cysticercosis indicate the existence of this parasite in the nervous system. The specificity of the reaction is conclusive when the Wassermann test is negative. If a more sensitive Wassermann test is carried out, reversal of the intensities can also be of value; in other words, a weak positive Wassermann test and a strong positive *Cysticercus* reaction indicate cysticercosis with a greater probability.

It should be remembered that the antigen's specificity in complement fixation reactions is only relative, and that its value can only be established on an empirical basis. For example, the antigens used for the Wassermann reaction are not by their nature specific, and yet the diagnostic value of the reaction is undeniable, although diseases etiologically different from syphilis can also give a positive reaction. Thus the specificity can only be established in terms of practical empirism. In respect to the *Cysticercus* antigen with which we have tested the reaction, it has been prepared in the form of alcoholic extract from all the parasite's integrative elements which constitute the aggressive agent to the tissue. In future investigations, the antigenic factor of the *Cysticercus* powder will be isolated, if possible. Yet now, the established correlations between the positiveness of the reaction and the presence of the parasite allows us to give a highly specific value to this diagnostic test.

Only three important points remain to be discussed: 1) The reaction's behavior in the three spinal fluid categories (lumbar, cysternal, and ventricular), 2) evolution of the reaction, and 3) the reaction's behavior in the blood.

1. It is of great importance to remember that the ventricular fluid is different in composition from the lumbar and cysternal fluids. In diseases of the nervous system which produce changes in the cerebrospinal fluid, the ventricular fluid can show few modifications or may even be normal. In ten cases of cysticercosis we have been able to compare the spinal and ventricular fluids. When a positive reaction was obtained with 0.2 cc. of lumbar fluid, 1 cc. of ventricular fluid was necessary to obtain positiveness of the reaction. The positive reaction with 0.5 cc. of lumbar fluid was always negative in the ventricular fluid. In only two cases was the reaction strongly positive in ventricular fluid. In one case a calcified *Cysticercus* in the third ventricle was found at autopsy. The cysternal fluids examined in 20 cases showed changes similar to those in lumbar fluids,

and at times even more marked changes due to the presence of *Cysticercus* in the cisterna magna. Since ventricular fluid examination is performed with greater frequency, especially in cranio-hypertensive cases, it is of great importance to remember that the changes in this fluid can be minimal or be absent.

2. In five cases the duration of the illness can be calculated as more than ten years. In one case the symptomatology had begun at the age of 11; when it was identified as cerebral cysticercosis by the spinal fluid examination, the patient was 37. Inflammatory changes in the spinal fluid had disappeared (2 cells per cu. mm., with 1 per cent eosinophils; total protein 20 mg. per cent; negative globulin reactions; Wassermann negative). The complement fixation test for *Cysticercus* remained positive with 0.2 cc. At autopsy no less than 30 parasites were found disseminated throughout the cerebrum. In two other patients in whom the diagnosis was confirmed at autopsy, the duration was 12 and 15 years, with the inflammatory changes in the fluid remaining and a very strong positive reaction for *Cysticercus*. At the psychiatric hospital two patients remain interned in which the evolution is 13 and 25 years, respectively; they present the typical changes in the spinal fluid. The reaction for *Cysticercus* in the fluid has been tested in these patients two or three times a year since 1943, and no decrease of intensity has been observed.

In spite of these data, it is reasonable to assume that, when the number of parasites is small, the inflammatory reaction will be weak. With time the parasites can become calcified and the inflammatory reaction can disappear. In these cases the fluid changes can regress and the complement fixation test can be negative. It is also true that some time must elapse from the moment the *Cysticercus* reaches the brain, causing symptomatology or not, until the complement fixation test becomes positive. We had the opportunity to examine a case in which a marked subcutaneous cysticercosis developed in two months. About the middle of the second month, the patient had a generalized epileptic seizure. The spinal fluid showed a pleocytosis of 19 cells, without other changes. The complement fixation for cysticercosis was negative. We believe that the process was in its initial phase and that the fluid changes were not yet typical. Unluckily, the evolution of this case was not followed, for it could have been used to establish the period of time required for the reaction to become positive.

3. The complement fixation test with *Cysticercus* antigen has been systematically tested in 12,220 blood serums over a period of 12 years. It was positive in 14.8 per cent of the population of the psychiatric hospital tested during this period. In the blood serum, the reaction maintains no parallelism with the Wassermann, Kahn, and Mazzini reactions. Of the 12,220 blood serums, 3,005 were positive for the Wassermann, Kahn, and Mazzini reactions, or 24.5 per cent. Of these 3,005 syphilitic serums, 785 were also positive for cysticercosis, or 26.2 per cent. Of the 9,215 negative syphilitic serums, 1,025 were positive for cysticercosis, or 11.1 per cent. Thus it can be seen that the syphilitic serologic changes increase the positive reactions to cysticercosis to a certain degree. But the facts that 73.8 per cent of the syphilitic serums were negative for cysticercosis and that there was 11.1 per cent of positive reactions for cysticercosis in non-

syphilitic serums show that this figure has immunologic significance. Would this indicate an extranervous infestation? This cannot be proved, but it is probable that this is so. The possibilities of infestation through fresh vegetables or by autoinfestation in taeniasis are quite numerous in certain populations.

From the practical point of view, it is important to stress that the blood serum reaction has very little value for the diagnosis of cysticercosis of the nervous system. Of all the nervous system cysticercosis cases identified by a positive reaction in the spinal fluid, the blood reaction was investigated in 114 cases. In 66 the reaction was positive and in 48 it was negative. In seven cases confirmed at autopsy the blood reaction had been negative.

TREATMENT

There is no effective treatment for cysti cercosis of the nervous system. In view of the favorable results obtained by Mazzotti and Hewitt[24] in onchocercosis with 1-diethylcarbamil-4-methylpiperazine chloride (Hetrazan), we have used this drug in two cases with a duration of less than two years, but have found no change in the symptomatology. Formerly we had employed antimony by the parental route without results. In some cases we have seen apparently good results with protein therapy.

When the symptomatology is evidently focal, the operative procedure is justified. Some cases of focal epilepsy have been treated successfully. In the craniohypertensive cases a decompressive craniotomy is justified; in some cases good results have been obtained and in others the process has worsened, depending on the inflammatory reaction which accompanies the process. At times operative procedures which will permit drainage of the cerebrospinal fluid are useful. Yet the indications should be carefully studied in each case, according to the symptomatic peculiarities. In cases of *Cysticercus* basal meningitis we do not have adequate therapeutic methods. Theoretically, one might consider the possibility of using cortisone or ACTH due to their inhibitory action on the growth of the connective tissue, but we have had no experience in testing these drugs.

SUMMARY

1. The frequency of nervous system cysticercosis is relatively high, especially in the population of Mexico on which this study is based.

2. The symptomatology is so varied that the clinical diagnosis is practically impossible. In 168 cases collected, the most frequent syndromes were: 1) generalized epilepsy, 2) intracranial hypertension of the cerebral tumor type, and 3) basal meningitis with mental disturbances predominating.

3. The diagnosis can be established with certainty by a cerebrospinal fluid complement fixation test performed with an antigen prepared with *Cysticercus* powder, as described here.

4. The degree of specificity, in terms of practical empirism, is no less than that of the Wassermann reaction.

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■ In cases of aura epileptica there is the greatest variety in the sensations felt, and the degree and the painfulness of the sensations are not such that we could explain by them the production of convulsions. It results from a thorough examination of a great many cases of aura, that we must admit that an unfelt irritation starts, at the same time as the aura, from some centripetal nerve, and is the real cause of the epileptic seizure. We will call this irritation an unfelt aura; and it would be well, indeed, if we could employ the name of "aura epileptica" for this unfelt irritation alone, so as to distinguish it completely from the vague and variable sensations which accompany it in many cases. There are facts proving that an unfelt aura may exist without any kind of sensation, either because the first effect of the irritation has been to destroy consciousness, or because the irritation does not start from sensitive nerve-fibres, but from centripetal nerve-fibres endowed only with the excito-motory power.

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Neuro-ophthalmologic Examination of Children

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THE NEURO-OPHTHALMOLOGIC EXAMINATION of children presents difficulties similar to those encountered in any examination in which cooperation from the patient is necessary. It is no harder to examine a cooperative child than it is to examine a cooperative adult, and an uncooperative individual is difficult or impossible to examine at any age. In testing the eyes of children, it is sometimes tempting to be less persistent or thorough than with adults, but actually a higher degree of effort and skill is required to obtain the information that is needed.

Before discussing these problems, it would be well to review the visual development of the human, especially in the early years, for the recognition of pathologic findings hinges largely on comparing the results of examination with the expected chronologic development of the child. Much of the following material is taken from Gesell and associates[1] and from Keeney,[2] who have written complete expositions of this subject.

VISUAL DEVELOPMENT

The *premature* keeps his eyes closed nearly all the time, but he may blink if a light is flashed, and occasionally one or both eyes may open. Eighth or ninth-month prematures are sufficiently developed to follow a dangling ring through a small arc.

A *full-term* newborn already has pupillary movements. If such reactions are present, conduction is intact along the visual pathways at least to the vicinity of the lateral geniculate bodies. The newborn is aware of dark and light. Opticokinetic nystagmus can be demonstrated.

During the *first month* the infant may gaze vacantly at his surroundings, but if a bright light is flashed, his bodily activity diminishes as though he were giving all his attention to the visual stimulus. He can follow an object through a 90-degree arc. Usually he pays no attention to objects farther than two feet away.

At about *six weeks* binocular fixation may begin, but even by the fifth or sixth month this may be variable, with lapses back to monocular fixation. At eight weeks the infant is very alert to moving objects and follows lights jerkily.

During the *third and fourth months*, both convergence and following movements are fairly well performed. This increased coordination and visual acuity are due not

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only to development of control of the extrinsic and intrinsic ocular muscles, but also to development of the macula. The latter progresses greatly during the third month. Full macular development is not complete until the age of six or seven years.

At six months the child resents a vertical prism and shows distaste for diplopia. He will fixate a string. At seven months binocular fixation is established but easily surrendered. At nine months depth perception is beginning, and the infant can play with tiny objects.

At ten months he may tilt his head back to look upward and he can fixate upon a 10-mm. object readily. At two years he seems to prefer red objects, but at two and a half years he prefers yellow and at three years blue. At six years he is aware of different shades of color.

At the age of five and a half years fusion is well established and accurate.

According to Keeney,[2] the normal visual acuity at four months is about 20/400, at one year 20/200, at two years 20/40, and at three years about 20/30; 20/30 to 20/40 vision on the Snellen chart is normal up to the age of four or five years.

THE NEURO-OPHTHALMOLOGIC EXAMINATION

The following observations in the neuro-ophthalmologic examination must be made: 1) visual acuity, 2) pupillary condition and reactions, 3) symmetry, parallelism, and movements of eyes and eyelids, 4) ophthalmoscopy, and 5) visual field examination.

Vision. In testing the vision of infants, the examiner should note the pupillary light reaction, whether blinking occurs in response to a bright light, and also whether the child fixates and follows a bright object. It is important to have an approximate knowledge of the patient's visual acuity. Up to the age of three years it is not ordinarily possible to be very accurate or certain as to the status of the vision. If the child is not too apprehensive and if he is handled gently, it may be possible to determine the visual acuity by the aid of marbles. If a marble of 1½-inch diameter is recognized at 20 feet, this indicates a visual acuity of 20/200; a ¾-inch marble recognized at 20 feet indicates 20/80 vision. Children of four, five, and six years of age cooperate well enough as a rule to permit the use of the E chart; the large plastic E held in the hand is often very useful. Sometimes the Snellen picture chart may be helpful, but the E chart is more accurate and just as easy for the small child. Once a child is familiar with the names of letters, he is usually very easy to test, since he is always eager to demonstrate his knowledge of the test letters.

Pupils. The pupils of prematures do not react well, and also the pupils are difficult to dilate widely. However, full-term infants have good pupillary reactions. Up to the age of three or four years the pupils may have slight inequality.

Muscles. Ocular deviations are often very difficult to diagnose when the child is four years old or less. Testing the ocular rotations requires a certain degree of cooperation. A small but nevertheless important amount of strabismus may be easily overlooked. The most valuable procedure in children of any age is to watch the eyes move as they follow the examiner's finger. The next most important is to employ the *cover test*, observing the ocular movements 1) at the time one or the other eye is being occluded, and 2) when the occluder is being removed. This has a good deal of value when used to diagnose ocular muscle palsies, in that the lag of the paretic muscle is quite easily seen as the affected eye moves out from under the cover. In children six years of age or more, the Maddox rod or red glass can be used to detect small abnormalities which may not be visible grossly. It is important to remember that the horizontal ocular muscles should be tested by having the child move the eyes first to one side and then the other, but that the vertical muscles should be tested only by

having the child move the eyes up and down from the position of far right lateral gaze or far left lateral gaze. The presence of an epicanthus or facial asymmetry should not mislead the examiner, since the alternating cover test will corroborate or dispel the impression of an ocular muscle abnormality. Ocular muscle palsies of recent onset cause diplopia. By using the cover test and the Maddox rod, the affected muscles are usually fairly easily identified. Congenital or non-neurologic ocular deviations are less likely to cause diplopia, and the paretic muscles do not usually follow the nerve distribution. Unilateral amblyopia is common if the deviation is one of convergence. It is well to bear in mind that a congenital Duane retraction syndrome may be mistaken for an ordinary abducens palsy. The former is often inherited as a dominant trait. On the affected side the eye retracts into the orbit, the palpebral fissure narrows, and the eye turns upward when looking *away* from the abnormal muscle. This syndrome is caused, not by a sixth nerve lesion, but by congenital fibrosis or dysinsertion of the ocular muscles. It may be bilateral.

There is no need to go into the subject of nystagmus, since nystagmus of children is in no way different from that of adults, except perhaps that of the rarely observed *spasmus nutans* in which the infant of less than three months of age develops nystagmus and head-nodding, and infants and children who have very poor vision may develop irregular wandering movements of the eyes.

Ophthalmoscopy. The ophthalmoscopic examination of infants up to the age of about six months is usually done quite easily without anesthesia, using 2 per cent Homatropine drops for dilating the pupil. It must be remembered that some lesions of importance are encountered in the peripheries of the fundi and, consequently, if these areas cannot be seen the examination should be repeated using rectal Pentothal sodium as anesthetic. Most childern of age five years or more can cooperate sufficiently for ophthalmoscopic examination. It is most advantageous to examine children up to age five years while they are lying down. If they are gently restrained by their parents to quiet their panic, many can be adequately examined without sedation.

In doing the ophthalmoscopic examination it is well to explore also the cornea, iris, lens, and vitreous with the +6 or +8 lens of the instrument, since many lesions may be easily overlooked when the examiner is eager to see the fundus and optic disk. The refractive error can be closely estimated by the following procedure: the ocular fundi are viewed with any lens that will give a clear image; then, while observing the disk, or preferably the fovea, the lenses are rotated in the ophthalmoscope toward the plus side until the image just blurs; the preceding lens then is the approximate refractive error. If this final lens is a plus lens, the eyes are hyperopic, and if a minus lens, the eyes are myopic. If the foveal reflex is elongated, there is often a considerable degree of astigmatism. All these errors can be accurately measured with the retinoscope by an ophthalmologist and proper glasses can be prescribed, if indicated. Glasses are ordinarily not prescribed for hyperopes unless the refractive error is greater than 2 diopters, since the vision may be 20/20 in spite of 4 or 5 diopters of hyperopia; the vision is always less than 20/20 in myopes, but glasses are not usually prescribed until school age is reached unless the myopia is greater than 3 or 4 diopters.

The ocular fundi of young children are somewhat different from those of adults, because development of the choroidal and retinal pigment and of the macula is still incomplete at birth. Children up to about the age of three years have pale disks. It is often difficult to decide whether the pallor is pathologic or normal. If optic nerve pallor is graded from 0 to 4, then one can usually consider a grade 1 pallor about normal for children up through the age of three years. As Walsh[3] has pointed out, there are

three major pitfalls in interpreting the infant's fundus: 1) an erroneous diagnosis of optic atrophy due to the gray color of the disk, 2) misinterpretation of the grayish appearance of the undeveloped macula, leading to a false diagnosis of macular degeneration or even of tumor, and 3) misinterpretation of the grayish peripheries of the retina as glioma, degeneration of the retina, or retrolental fibroplasia.

The differential diagnosis of elevated optic disks is an interesting and important one. It might be well here to discuss the method of measurement which gives the most accurate readings and permits reliable consecutive examinations. This method is the same as is used to measure the refractive error. It neutralizes the examiner's accommodation. The disk is brought into focus, and then the lenses are rotated toward the plus side until the very topmost portion of the disk blurs out; the preceding lens is then the height of the elevation. This lens is then left in place, the light is thrown on the macula, and then the lenses are rotated toward the minus side until the fovea barely comes into focus. The difference between the two lenses is the elevation of the disk in diopters.

The problem of correct diagnosis of elevated optic disks is complicated by the many congenital variants. These include structurally full disks, tilted disks, and disks containing hyaline bodies; it must be remembered that tilted disks produce superior temporal field defects which may lead to an erroneous diagnosis of a chiasmal lesion, and hyaline disks may involve mild to marked visual field defects, usually of an arcuate character.

True papilledema may be due to increased intracranial pressure (so-called "choked disk"), hypertension, septic conditions, increased protein in the spinal fluid, optic neuritis, orbital lesions, and other causes. These can almost invariably be differentiated by ophthalmologic examination alone.

Visual fields. The visual fields are not very reliably tested in children younger than seven or eight years, since so much depends on subjective findings. The occasional child of six years may give satisfactory cooperation, but on the whole most children must be eight years of age or older before their visual field defects have *localizing* value. The author has in mind two bright little girls, one aged four years and 11 months and one aged five and a half years, both of whom were excellent subjects. Each had an astrocytoma of the optic chiasm. However, the gross examination of the visual fields of children even of six months of age or less may give findings of relatively reliable *lateralizing* value. Thus, if the movement of a bright light or interesting object, such as a nursing bottle, fails to elicit a response on one side but produces a good response on the opposite side, this may well be significant as indicating a homonymous hemianopsia. Watching the facility of grasping objects placed alternately on the two sides sometimes is of value. Near the age of six years it is possible to gain some idea as to the presence of relative defects or those which do not quite involve the entire half-fields, but the gross testing by confrontation is often as accurate as the use of the perimeter or tangent screen. However, even at this age it is well to try to test children on the perimeter or tangent screen if field defects are suspected. The author has not had experience with flicker perimetry on children and, consequently, does not know whether it has value.

It is important in young children to complete the testing as rapidly as possible, since their powers of concentration are poor and they tire easily. Unless the field technician is one of great experience and tested reliability, it is wise for the physician to do his own testing. Otherwise, the child may be too tired to give good responses when the field is rechecked. Sometimes it is more accurate to carry out this examination in two or three half-hour sittings. Inability to fixate the target is the major limiting factor in testing the visual fields accurately in chil-

dren. Hence, as in adults, it is highly important to have about 7 foot-candles of illumination in the examining room, so that the examiner can watch the position of the patient's eyes and thus assess the reliability of the answers given. The so-called fluorescent or dark-screen examination of the visual fields does not take into account this difficulty, which about 15 per cent of adults share with children.

Once the field defects have been plotted, their interpretation ordinarily poses no great additional problem so far as the location of the lesion is concerned. The same cannot be said with reference to the nature of the lesion responsible for the field defects. The more the field defects differ in the two eyes, the more anterior is the situation of the lesion in the visual pathways; and conversely, the more similar (congruous) the defects, the closer is the lesion to the visual cortex. Thus, a field defect in one eye but not in the other can result only from a lesion in the homolateral eye or optic nerve. A defect with an arcuate character and with a split in the nasal field results from a lesion in the eye or orbit. If the split is found in the vertical midline, the lesion must be intracranial. The classic chiasmal defect is bitemporal hemianopsia, but chiasmal defects have such infinite variety that it is impossible to present them all. Any field defect which has a midline vertical split in one eye which is not fairly closely duplicated in the other eye must be suspected of being due to a chiasmal lesion. Anterior temporal lobe defects are often quadrantic because of the arrangement of fibers in the optic radiations. Posterior temporal lobe defects are usually quite congruous but are without macular sparing. Occipital lobe field defects are exactly superimposable in the two eyes, are often scotomatous, and often have macular sparing.

SUMMARY

In summary, among children as among adults, it is necessary to make use of all the help possible in arriving at a diagnosis. In the neuro-ophthalmologic portion of the examination, this includes measurement of the visual acuity, observation of the pupils and ocular movements, and ophthalmoscopic and visual field examinations.

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CASE REPORT

Chronic Hypoventilation in an Epileptic Patient

Charles E. Wells, M.D.

SINCE THE EFFECTS of hyperventilation were first described by Rosett[1] and Foerster,[2] it has been known that the epileptic patient is profoundly sensitive to changes in respiration, especially to hyperpnea. A search of the literature fails to reveal any case report in which a chronic respiratory abnormality has been found in a patient subject to seizures. For this reason the present case is considered to be of interest.

CASE REPORT

A 19 year old white man began to experience seizures at seven years of age. As a child he had a number of rather severe illnesses, none of which appeared to bear any relation to the onset of seizures. The seizures consisted of brief episodes of loss of contact with his environment, with staring or blinking of the eyelids, sometimes accompanied by head nodding and bilaterally symmetric jerks of the upper extremities. At age 14 he began to have rare generalized convulsions, characterized by prolonged loss of consciousness, clonic movements of all extremities, chewing motions of the mouth, and tongue biting. At the time of his admission to the Clinical Center of the National Institutes of Health, the patient was having approximately 20 to 40 minor seizures daily. Major seizures occurred once or twice yearly.

Pneumoencephalograms had been done at another hospital shortly before his admission and revealed no abnormalities. Various drugs had been tried singly or in combination, including Dilantin, phenobarbital, Mebaral, Mesantoin, Tridione, Paradione, Phenurone, Gemonil, Milontin, Mysoline, Hibicon, and bromides. None had controlled the seizures with any degree of success.

The patient was an alert, well-developed young man of normal intelligence. No significant abnormalities were found on neurologic examination or on general physical examination. Chest and skull roentgenograms were interpreted as normal. Urinalysis, hematologic studies, blood urea nitrogen, and liver function studies were within the range of normal.

Electroencephalograms (figure 1A) showed paroxysmal discharges appearing bilaterally synchronous and symmetric over the two hemispheres, with maximal amplitude over the frontal regions. The discharges consisted of 2.5 to 3 per second wave-and-multiple-spike complexes of very high voltage and of long duration, lasting as long as 220 seconds in the resting state. The background activity was well regulated and symmetric. Repeated electroencephalograms with repeated periods of hyperventilation revealed that the patient was extremely sensitive to this test. During five minute periods of hyperventilation, the electroencephalogram routinely showed evidence of markedly increased activity (figure 1B) and frequently showed paroxysmal bursts of epileptiform activity lasting 90 per cent or more of the hyperpneic testing period.

Repeated blood electrolyte determinations were performed (table 1) which showed the patient's venous serum carbon dioxide content (Van Slyke and Neill method[3]) to be above the range of normal. Arterial pH was 7.43 and 7.46 on separate occasions. Repeated de-

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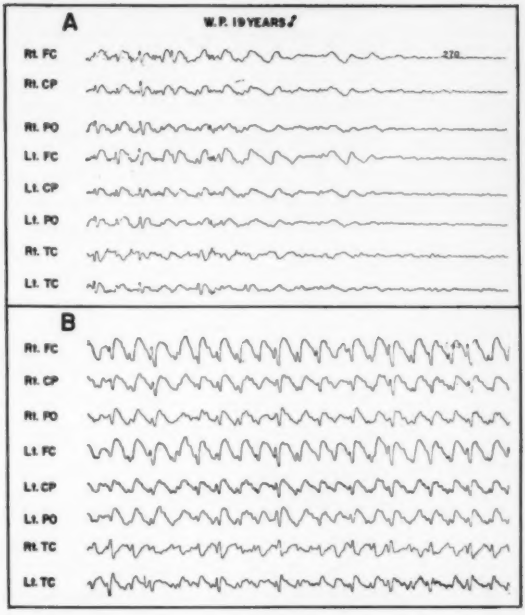

FIG. 1. Electroencephalogram in a 19 year old epileptic. *A* resting record. *B* with hyperventilation.

terminations of serum sodium, potassium, and chloride consistently revealed normal levels.

Following discovery of an elevated carbon dioxide content in the blood of this patient, respiratory function studies were done to determine minute volume of ventilation. On one occasion, it was found to be 5.88 L. per minute BTPS and on another, 4.24 L. per minute BTPS. Average normal minute ventilation for a person of the patient's height and weight is 6.77 L. per minute, with the lower limit of normal being 5.84 L. per minute BTPS. The patient showed no evidence whatever of lung disease, and vital capacity was normal.

It is of interest that during this patient's hospital stay he was given Diamox (750 mg. per day in divided doses) in an attempt to alleviate the seizures, but seizure frequency was unaffected. Electroencephalograms taken while the patient was receiving Diamox consistently revealed sensitivity to hyperventilation identical to that before Diamox was begun and before changes in pH and carbon dioxide content were induced (table 1). It is significant that, though the total carbon dioxide content fell during Diamox therapy, there was no significant change in dissolved carbon dioxide as carbonic acid or in carbon dioxide tension.

DISCUSSION

In 1924 Rosett[1] first described the production of seizures by hyperventilation in several patients with known or suspected epilepsy, and he advocated it as a diagnostic tool. In the same year Foerster[2] tested the effect of hyperventilation in 45 patients with epilepsy. In 25 of these patients a seizure resulted which, on repetition, was shown to occur with varying degrees of consistency in the individual patient. A number of papers followed confirming the clinical usefulness of hyperpnea as a diagnostic method in epilepsy.

It followed logically that interest developed as to the physiologic mechanism involved in the production of seizures by hyperventilation, and to what extent this might be related to the usual seizure mechanism in epileptic patients. In 1928 Lennox[4] studied the bicarbonate in the blood of 100 seizure patients. Taking a range of

TABLE 1
LABORATORY STUDIES

	CO_2 Content (mEq./L.)	H_2CO_3* (mEq./L.)	$BHCO_3$* (mEq./L.)	CO_2 Tension† (mEq./L.)	pH	Chlorides (mEq./L.)
Venous Blood IP						
Normal values	26 to 33	1.35	24.65	46	7.35 to 7.5	99 to 110
Patient resting	33 to 35	1.4	33.6	46	7.48	103 to 105
Patient during Diamox therapy	25 to 28	1.4	24.6	47	7.34	108 to 113
Arterial Blood						
Normal values	25 to 33	1.1	23.9	40	7.35 to 7.5	
Patient resting	30	1.25	28.75	41.5	7.46	
Patient during Diamox therapy	22‡	1.15	20.85	38	7.36	

IP—Serum sodium and potassium remained within normal limits (136 to 146 mEq./L. and 3.5 to 5.5 mEq./L. respectively) both before and during Diamox therapy.

*Calculated from: $pH = 6.1 + \log \frac{BHCO_3}{CO_2}$

†Calculated from: $pH = \frac{\text{Total } CO_2 \text{ as } H_2CO_3}{0.0672}$

$0.0672 = \frac{100 \times 0.51}{760}$ where 0.51 = solubility coefficient of CO_2

‡Not determined. Figure estimated from drop in venous CO_2 content with Diamox therapy.

55 to 70 vols. per cent (24 to 31 mEq./L.) as normal, nine patients had levels above normal. The average carbon dioxide for epileptic patients was 64 vols. per cent (28.5 mEq.) compared with an average of 59 vols. per cent (26 mEq.) in normal patients. Gibbs, Lennox, and Gibbs[5] reported carbon dioxide determination in arterial and internal jugular venous blood samples in 94 patients subject to seizures. They found abnormalities in 70 per cent of these patients, noting that in general the carbon dioxide tended to be abnormally low in patients with petit mal, whereas the carbon dioxide was abnormally high in those with grand mal. They suggested that a deviation of the arterial carbon dioxide might be due to some disturbance in respiration, but they did not elaborate on this suggestion. Lennox and Gibbs[6] found the arterial oxygen saturation to be below normal in 46 per cent of 88 patients with epilepsy and also in 45 per cent of patients with other neurologic diseases. They considered that this was probably of insufficient degree to produce seizures, and again the suggestion was raised that this might be due to abnormal pulmonary ventilation.

Within a few years of Rosett's and Foerster's first observations on hyperpnea, Lennox[7] had made hundreds of graphic records of the pulmonary ventilation of epileptic patients. He noted that they showed a marked irregularity in the rate and depth of breathing, but he did not characterize the abnormality further. The same author[8] also showed that increasing oxygen tension of inspired air would decrease the effect of hyperventilation, as would increasing the carbon dioxide content of the inspired air. As noted above, Gibbs, Lennox, and Gibbs[5] suggested that certain abnormalities of blood gases also might be due to some sort of respiratory abnormality.

Cobb and co-workers[9] recorded the respiratory pattern and minute respiratory volume in six epileptic patients (petit mal type) while making electroencephalographic recordings. In three of these patients they were able to show a marked increase in

electroencephalographic abnormalities when the minute volume of respiration rose above normal. They noted that many of the attacks were definitely preceded by short bursts of spontaneous hyperventilation. In 1947 Teglbjaerg and co-workers[10] found that hyperventilation increased the number of petit mal attacks in epileptics even when they were breathing high concentrations of carbon dioxide. They concluded that hyperventilation has in itself an ictogenic effect not dependent entirely on the ictogenic effect of carbon dioxide expiration.

None of the previously mentioned findings, however, explain why hyperventilation produces seizures in susceptible persons — whether it is due to a sequence of orderly changes or to a medley of apparently unrelated changes. Investigators turned to studies of the blood pH for an explanation. It was shown[11] that blood pH was within the normal range in patients with epilepsy. Nims and co-workers[12] demonstrated that, compared to the normal individual, the patient with petit mal epilepsy is not as able to control adequately or adjust quickly the acid-base balance when it is disturbed by overventilation. Davis and Wallace,[13] however, studying normal male subjects, were unable to show that metabolic alkalosis (pH up to 7.64 before hyperventilation) or acidosis (pH down as low as 7.29 before hyperventilation) caused any significant change in the effect of hyperventilation on the electroencephalogram.

These same authors felt the blood sugar level to be of considerable importance with respect to the electroencephalographic effects of hyperventilation. They considered that a low blood sugar favors the appearance of delta waves with hyperventilation and that a high blood sugar strongly tends to prevent their appearance. Schwab[14] agreed with the critical importance of the blood sugar level in assaying the effects of hyperventilation. It must be understood that these authors were discussing the effects of hypoglycemia on the delta waves which appear with hyperventilation in some normal subjects and not the effect of hypoglycemia on the seizure pattern which appears with hyperventilation in some epileptic subjects.

In the patient here presented, an electroencephalographic recording was made after an 18-hour fast with a blood sugar level of 53 mg. per cent (normal, 65 to 110 mg. per cent in this laboratory by the Nelson[15] and Somogyi[16] methods) and one hour after a high carbohydrate meal with a blood sugar level of 152 mg. per cent. No significant difference between the resting record and the response to hyperventilation could be noted between the two records.

In 1930 Wolff and Lennox,[17] studying the cerebral vessels in the cat, showed that hyperventilation induced a constriction of cerebral arterioles. In 1935 Gibbs and coworkers,[18] using a thermoelectric blood flow recorder inserted into the internal jugular vein, reported that hyperventilation resulted in a sudden and pronounced decrease in blood flow through this vessel in ten of 13 patients. Gibbs, Gibbs, Lennox, and Nims[19] later found that in subjects whose brain waves were not slowed by hyperventilation there was little decrease in the internal jugular carbon dioxide content with overbreathing, whereas in two subjects whose brain waves were markedly slowed by hyperventilation there was a marked decrease in their internal jugular carbon dioxide content with overbreathing. They interpreted this to mean that, in those subjects in whom hyperpnea produced profound electroencephalographic changes, the cerebral arterioles did not constrict with hyperventilation to the same extent as normal.

In 1946 Kety and Schmidt,[20] using the nitrous oxide method, showed that cerebral blood flow was regularly diminished by hyperventilation in the normal individual. Further studies in the same laboratory[21] revealed cerebral blood flow in epileptics in the resting state to be the same as in normal individuals. They further showed that with hyperventilation the cerebral blood flow in epileptics decreased to the

same extent as in normal subjects. These studies were done on patients with grand mal seizures. These findings were confirmed by Gibbs and co-workers[22] using an Evans blue constant dye injection method. No reports of cerebral blood flow studies in petit mal subjects have been found.

Thus, while data indicate no significant difference between epileptic subjects and normal subjects in total response to hyperventilation, they do not, as pointed out by Wolff,[23] necessarily indicate whether or not there may be minor local changes in the cerebral circulation of importance.

The question has gradually evolved whether it is cerebral hypocapnia or cerebral anoxia which precipitates the seizures in response to hyperventilation. Gibbs and co-workers[19] hold that the former is the factor of significance. They consider the cerebral arteriolar constriction which occurs with hyperventilation to be a protective mechanism to prevent cerebral hypocapnia and the slow waves which appear to be due to a drop in carbon dioxide. They, together with Engel and co-workers,[24] do not believe the cerebral anoxia which occurs is sufficiently significant to explain the changes. In 1942 Davis and Wallace[13] found that hyperventilation with oxygen instead of atmospheric air produced less alterations in the electroencephalogram. This they interpreted as meaning that the delta activity induced by overbreathing was due to cerebral anoxia consequent to cerebral vasoconstriction. Lloyd-Smith,[25] finding the slow waves which occurred with hyperventilation to cease with sudden self-induced apnea only to recur again in 30 to 60 seconds, likewise considered cerebral anoxia to be the decisive factor. Lennox and Cobb[8] have reported a patient who always had a seizure with two minutes or less of hyperpnea when breathing atmospheric air, but required a longer period of hyperpnea when breathing oxygen. This same view was held by Grant and co-workers[21] on the basis of their cerebral blood flow studies. The findings of Teglbjaerg and co-workers[10] previously mentioned would also contribute to this view.

In the patient under discussion, we have no proof as to the cause of the marked electroencephalographic changes with hyperpnea. It might be inferred, however, that the changes are not due to hypocapnia, since reduction of the patient's venous carbon dioxide to 25 mEq./L., as produced by Diamox, in no way affected his seizure frequency or his response to overbreathing.

The patient reported here was exquisitely sensitive to hyperventilation, consistently responding to this exercise with occurrence of seizures. In this particular patient, however, the body appeared to have adjusted to this lability by chronic underbreathing.

The possibility of preventing seizures by hypoventilation occurred to Vujic a number of years ago, and in 1933 he reported the results[26] in five patients in whom he had induced chronic hypoventilation by means of artificial pneumothorax. In all five patients he noted a decrease in frequency of seizures, sometimes striking, during the maintenance of bilateral pneumothorax. Two years later Slivko and Torkanovskii[27] reported their results in four patients with major or with minor seizures treated with bilateral pneumothorax. They reported excellent results in three of the four patients so treated, with a decrease in the number and severity of seizures. They also reported another case of an epileptic patient who developed bilateral pulmonary tuberculosis, whose epilepsy showed striking improvement after institution of bilateral pneumothorax. That this is not the only result of artificial pneumothorax was well demonstrated by the findings of Bertrand and co-workers,[28] who showed significant electroencephalographic abnormalities occurring with the institution and maintenance of artificial pneumothorax in a series of tubercular patients without epilepsy.

The patient reported here was shown to have a minute respiratory volume below or at the lower level of normal on repeated testing. A review of the literature, though

replete with references to the relationship between seizures and respiration, did not reveal a case report of any chronic respiratory abnormality in an epileptic patient. This patient's high arterial carbon dioxide was consistent with his decreased minute ventilation, that is, he ordinarily did not breathe deeply enough to blow off carbon dioxide and to keep it at a normal level in the blood. One may conjecture that in this individual the body unwittingly acted to overcome the sensitivity to hyperventilation by keeping the minute volume of respiration below normal.

SUMMARY

1. A case is reported of an epileptic patient, quite sensitive to the effects of hyperventilation, in whom the arterial and venous carbon dioxide was elevated and the minute volume of respiration was abnormally low.

2. A review is made of the literature concerning the relationship of pulmonary ventilation and the carbon dioxide content of the blood to epilepsy.

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CASE REPORT

Raeder's Paratrigeminal Syndrome

Gerald H. Klingon, M.D. and William M. Smith, M.D.

THE TERM "paratrigeminal syndrome" was introduced by Raeder[1] to designate a "limited space" in which he could localize certain intracranial lesions producing ocular sympathetic palsies. The syndrome itself consists of involvement of one or more cranial nerves, in addition to the ocular sympathetic. Because the trigeminal nerve was most often involved in the complex, Raeder termed the syndrome "paratrigeminal," without actually defining the so-called "limited space." The ocular sympathetic paralysis results in a Horner's syndrome, which consists of ptosis and miosis but not anhidrosis. Anhidrosis would not be a feature because the fibers subserving vasomotor function of the face course with the external carotid artery and its branches. Thus, an intracranial lesion could only involve the internal carotid plexus and its subordinate plexuses, resulting only in ptosis and miosis. Each of Raeder's six cases had one or both of these. The exact nature of the lesion was demonstrated in only one of the cases and this proved to be an endothelioma (meningioma) involving the gasserian ganglion, the motor portion of the trigeminal nerve, and the abducens, oculomotor, and trochlear nerves, as well as the sensory portion of the trigeminal nerve and the internal carotid artery, apparently in its intracavernous course.

Raeder was correct in concluding that such a lesion would produce a Horner's syndrome without anhidrosis, but his designation of the paratrigeminal area as the anatomic origin of such a syndrome may be somewhat inaccurate. There are several reasons for questioning the accuracy of his conclusion.

Inspection of Raeder's diagram (figure 1) indicating the position of the tumor shows clearly that the actual site of the mass was the middle fossa and that only the posterior margin of the neoplasm lay on the petrous pyramid. Therefore, the term "paratrigeminal" seems superfluous because the lesion was in a position to, and indeed did, impinge upon the nerves and artery generally associated with the cavernous sinus syndrome.[2] Secondly, the relationship of the internal carotid artery to the gasserian ganglion, lying in the semilunar impression of the petrous pyramid, makes a "paratrigeminal" entity unlikely. Figure 2 shows this relationship by means of rubber tubing placed snugly in the carotid canal. Since the tubing is larger than the carotid artery and is tightly placed, the idealization of the figure errs on the side of the authors' contention, for it can be seen that the artery is somewhat more deeply placed than the semilunar impression. Thus a lesion could involve both struc-

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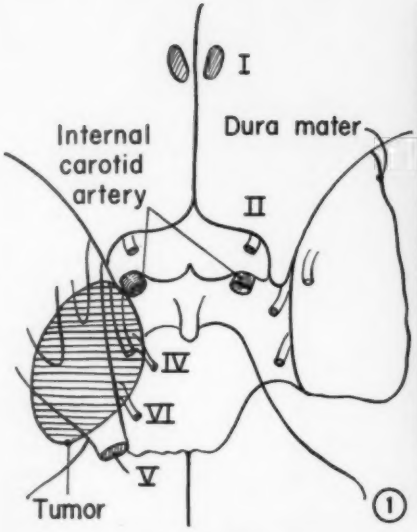

FIG. 1. Adaptation of the diagram which appears in Raeder's article. Note that the tumor mass actually lies in the middle fossa and involves the cavernous sinus.

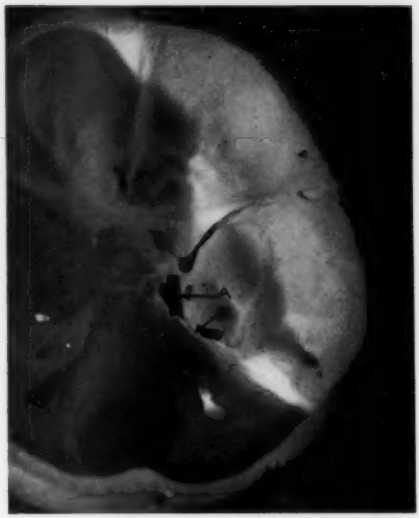

FIG. 2. The base of the skull viewed from above, showing the internal carotid artery (*A*) and the semilunar impression for the gasserian ganglion. (*B*).

tures either by eroding the petrous pyramid or by extension into the medial aspect of the middle fossa, but in either case it would not be confined to a so-called "paratrigeminal" region. Another objection to the anatomic designation is that it does not consider the implication of inflammatory disease in the production of syndromes not materially different from the one which Raeder described. This must be considered the major objection, for it is not merely an academic issue but one which affects management of the patient.

Inflammation may present as multiple lesions or it may extend in continuity. Therefore, an inflammatory lesion which affects the intracranial sympathetic pathway may also extend to, or discretely involve, the external pathway. The authors recently observed a case which illustrates this point, since the patient's presenting signs satisfied the criteria for a diagnosis of the paratrigeminal syndrome; yet she had facial anhidrosis, as well. For this reason, and because the case raised questions as to pathogenesis and management, it is being reported.

CASE REPORT

A 45 year old Public Health Service nurse was admitted to the hospital on October 14, 1954. Three weeks prior to admission she noted pain in the right eye and the right forehead, as well as "swelling" of the right eye. This was progressive. At the same time the patient had rhinorrhea and nasal congestion. She was treated for this without relief. Re-examination at the hospital where she was employed revealed the swelling to actually be ptosis. She was, therefore, referred to the neurology clinic at the U. S. Public Health Service Hospital, Staten Island.

Examination of the patient revealed a right Horner's syndrome, including miosis, ptosis, apparent enophthalmos, conjunctival injection, and relative anhidrosis of the right forehead. Hypalgesia and hypesthesia were present in the distribution of the ophthalmic division of the trigeminal nerve on the right. The right corneal sensation and response were diminished, although tenderness of the globe was present. The patient also had tenderness over the right

antrum and frontal sinus, as well as purulent nasal discharge. The remainder of the physical and neurologic examination was within normal limits.

Laboratory findings. The white blood count, hemoglobin, hematocrit, and sedimentation rate were all within normal limits. The serologic test for syphilis was negative. Urinalysis revealed a trace of reducing substance. A two-hour postprandial sugar was 120 mg. per cent. Fasting blood sugar was 132 mg. per cent. Cerebral spinal fluid showed 25 mg. protein and four cells per cu. mm., type unspecified. Roentgenograms of the skull, including basal views, were negative. The sinuses were reported clear.

Course. The patient's course was one of gradual improvement in symptoms and signs, except that in the second week of hospitalization tenderness over the right common carotid artery was found. During her stay instillation of 4 per cent cocaine produced 2 mm. of dilatation in each pupil, whereas epinephrin in concentrations of 1 to 2,000 and 1 to 1,000 produced no change in pupillary size. Ophthalmometry did not support the impression of enophthalmus. A starch-iodine test revealed relative anhidrosis over the right forehead (figure 3). At the time of discharge on November 3, 1954 the patient had minimal ptosis and miosis, slight anhidrosis, and her sensory deficits had almost disappeared. The carotid tenderness had also disappeared. She now complained of more generalized headache of tension type. The patient was seen periodically for two months as an out-patient. During this time her signs and symptoms abated still further. At the end of this time she had only slight miosis remaining. Her headaches, which were of different type than the admission complaint, were apparently related to a severe emotional problem, and these abated with ventilation and reassurance.

FIG. 3. The patient during a starch-iodine sweat test, showing the relative anhidrosis of the right forehead, miosis, and ptosis.

DISCUSSION

The criteria for diagnosis of Raeder's paratrigeminal syndrome include involvement of 1) the pupillary-tarsal sympathetic fibers, and 2) the ipsilateral trigeminal nerve, among others. Anhidrosis is not included because the vasomotor fibers to the face course with the external carotid artery and its branches. Our patient's case satisfied these criteria, except for the fact that she had facial anhydrosis. Since no single lesion could produce the complex of ophthalmic neuropathy and a Horner's syndrome with anhidrosis, it would be fair to state that involvement of each of the affected pathways would be difficult to localize. The ophthalmic nerve might suffer insult at any point in its intracranial course, at its inception in the posterior fossa, in the cavernous sinus, or at the superior orbital fissure. The vulnerability of the ocular sympathetic pathway is even greater in terms of its longer course. Therefore, it is felt that an attempt to implicate a single site would be difficult, if not impossible. It seems much more likely that our patient had either multiple or widespread extension of inflammatory lesions. The tenderness over the right common carotid artery, as well as the facial anhidrosis, supports this likelihood.

The foregoing would seem to necessitate a broader view of the syndrome, inasmuch as the patient's signs closely resembled a clinical pattern heretofore described as a highly localizable entity, although she evidently had rather widespread lesions. The need for reappraisal of this syndrome is further borne out by Walsh's[3] cases and Be-

drossian's[4] case, all of which were self-limited Since they were self-limited, no definite statement may be made as to etiology but, speculatively speaking, inflammatory or postinflammatory states must be considered. However, speculation as to etiology is not as important as the fact that the cases underwent spontaneous regression. The regression of signs must perforce cast a different light on Raeder's contribution, not only because the pathogenesis of a given case would be statistically non-neoplastic, but because management of the case would be altogether different. This is so because a diagnosis of tumor in such a syndrome is less likely, and hence implies that conservative management is indicated. Furthermore, when the onset and course of the process suggest neoplasm, an anatomic localization to the middle fossa seems more appropriate.

The self-limitation of our case, as well as those described by Walsh[3] and Bedrossian,[4] suggests that a reasonable approach to proper management is watchful waiting and reassurance of the patient. If onset is very gradual and signs and symptoms progress during the period of observation, arteriography or air study would be indicated. On the other hand, if no progression has ensued beyond the initial findings, the ancillary studies should be withheld. On the basis of past experience the probability is that, when one is confronted by a case with the features described herein, one is dealing with a self-limited entity of unknown etiology. The clarification of this particular aspect of the "paratrigeminal syndrome" is the main purpose of this paper.

SUMMARY

1. A case of so-called paratrigeminal syndrome is presented.

2. The case differed from previously reported cases in that facial anhidrosis was present.

3. Objections to the use of the term "paratrigeminal syndrome" are presented.

4. The proper management of such cases is discussed.

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2. Hausman, Louis: Personal communication.
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■ A great many cases in which, by various means, the aura epileptica has been prevented from going up to the encephalon, show that the fit is very often due to a simple outside irritation. Applications of ligatures, sections of nerves, amputations, act in this way. We might say the same thing of the elongation of muscles (the first ones that are convulsed), and, in a certain measure, of various means of revulsion (such as burning, blistering) although the principal mode of action then consists in producing, by a reflex action, a change in the nutrition of the nervous centres, and of the nerves which are the channels of the aura.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

DIAGNOSTIC NOTE

Diagnosis and Localization of Herniated Intervertebral Disks

*George Zervopoulos, M.D., Ph.D.**

HERNIATED INTERVERTEBRAL DISKS often fail to give clinical symptomatology corresponding to the exact anatomic level. This is especially true in the case of disks in the L4-L5 and L5-S1 interspaces. In some cases false localizing signs may further obscure the proper diagnosis. In addition, myelography at times fails to confirm the clinical diagnosis, although the lesion may be subsequently demonstrated at surgery. The author studied 62 cases in a search for more accurate diagnostic signs. Sixty of the cases exhibited herniated disks in the L4-L5 or L5-S1 interspaces. All patients were subjected to surgery.

L4-L5 herniated disks (lateral herniations, 20 cases; central herniations, 12 cases). The convexity of the scoliosis, which is expected to be toward the side of the rootlet involvement, was observed in 13 of the 20 cases with laterally herniated disks. Six of the 12 patients with central disks were found to have the convexity of the scoliosis toward the predominant side of rootlet compression. In four cases there was no scoliosis. The anticipated weakness of dorsiflexors of the great toe was present in only 11 cases, while the ankle jerk was preserved in only 18 subjects. Myelography demonstrated the lesion in 28 cases and was nonconclusive in four cases.

L5-S1 herniated disks (lateral herniations, 15 cases; central herniations, 11 cases). Scoliosis with the convexity toward the opposite side of the lesion, as is to be expected, was found in only nine of the 15 cases with laterally herniated disks. In six central herniations, the convexity of the scoliosis was noted toward the side with the lesser rootlet compression. Scoliosis was absent in four cases. The expected weakness of plantar flexion in the great toe was present in only seven cases. The ankle jerk was reduced in only 20 cases. The myelogram was indicative of the lesion in 18 cases, nonconclusive in six, and completely negative in two. Superficial sensory loss was demonstrated in the majority of both L4-L5 and L5-S1 cases.

The author found that diminution in vibration sense was the most reliable finding for a sharp localization. He noted homolateral reduction of vibration sense in the internal malleolus in all cases of herniations corresponding to L4-L5 interspace, and in the external malleolus in all cases of L5-S1 herniations. In instances of L4-L5 herniations occurring centrally, vibration sense was absent in both internal malleoli, while this sense was absent in both external malleoli in the presence of central herniations in L5-S1.

Thus in all 60 cases in this series the alterations in vibration sense correlated with the location of the herniations at L4-L5 and L5-S1 as demonstrated in surgery. The remaining two patients in this series complained only of back pain. They exhibited a loss of vibration sense in both patellae, and laminectomy revealed herniation in the L3-L4 level.

*Neurologist and psychiatrist, Thessaloniki, Greece.

This article was abstracted and translated from Hellenic Medicine (24:595, 1953) by John Logothetis, M.D., University of Minnesota Medical School, Minneapolis.

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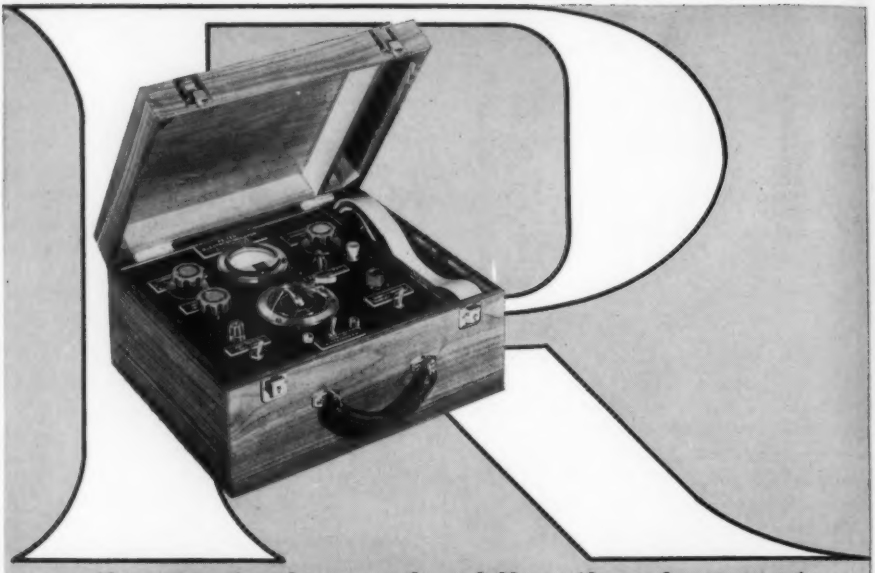

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OCTOBER, 1956

Membership Drive Remains in High Gear

The campaign to develop an increasing cross-fertilization of talent in the AAN membership continues at a high pace, averaging about 50 new members a month. During the month of August 69 additional members were added to the AAN list. These 69 new members (all categories) are: Norman Allen, Paul J. Anderson, James B. Arey, N. L. Auckland, Betty Q. Banker, Charles F. Barlow, Luis Barraquer, Donald R. Bennett, Claude Bertrand, Mary A. B. Brazier, H. F. Cameron, Hatai Chitanondh, Julius H. Comroe, Jr., Tillye Cornman, Peter L. Eichman, Frank H. J. Figge, Karl Frank, Milton J. Freiwald, Louis S. Goodman, David M. Gould, Joseph Barnett Green, Raymond F. Hain, Max Hamburgh, Guillermo Hernandez, Hudson Hoagland, Howard Holtzer, Beni Horvath, H. H. Hyland, Francis Eugene Kulcsar, Edward W. Lauer, Irvine M. Levine, Edward A. Liske, Jr., R. B. Livingston, George J. Lucas, Bernard J. Michela, Walter A. Mickle, Monica Millitzer, James Preston Myers, Harold J. Nicholas, Carl C. Pfeiffer, Marvin Posner, James W. Rae, Jr., Jean Rey-Bellet, Eugene Roberts, E. Douglas Rooke, Gilbert S. Ross, Peter T. Rowley, Ernest Sachs, Jr., Konstantin Scharenberg, Francis O. Schmitt, Jacob Silberman, Walter R. Slade, Jr., Caswell King Smith, David E. Smith, John A. Stern, Thomas J. Stuart, Roy L. Swank, Rhett Talbert, Ira R. Telford, Clinton H. Thienes, James F. Toole, Edward F. Vastola, Carmine T. Vicale, Jose Maria Vilanova, Joseph C. White, Thomas L. Willmon, J. Walter Wilson, Harold G. Wolff, and M. Wolman.

Principal Types of AAN Membership and Methods of Application

The principal types of AAN membership are fellows, active, associate, and junior members. Fellowship and active membership in the Academy are open to diplomates in neurology of the American Board of Psychiatry and Neurology, or to those certified in neurology by the Royal College of Physicians and Surgeons of Canada, who have been sponsored by two fellows or active members of the AAN. Junior membership is open to graduates of class A medical schools, who are in residency training in neurology. Eligible for associate membership are those in advanced training in clinical neurology and physicians in other clinical fields or neurologic scientists who have made a contribution to the advancement of our knowledge of the nervous system.... Candidates for active or junior membership, with the proper sponsorship, should apply to Mrs. J. C. McKinley, AAN Executive Secretary, 3501 East 54th Street,

Minneapolis 17, Minn. Candidates for fellowship or associate membership should apply to Dr. Pearce Bailey, Chairman, AAN Membership Committee, National Institute of Neurological Diseases and Blindness, Bethesda 14, Md.

Neurochemists Meet in Denmark A group of about 120 distinguished scientists interested in the chemistry of the nervous system convened in Aarhus, Denmark, for the Second International Neurochemical Symposium (July 23-27). Topic of the symposium, which consisted of five full-day sessions, was "The Metabolism of the Nervous System." The presentations ranged from the composition and electron microscopy of the nervous system to the metabolism of portions of the nervous system and of the whole brain, from the blood-brain barrier to the metabolism of isolated biochemical processes or systems. Also there were excellent reviews on important aspects of neural metabolism and chemical pharmacology. In the words of Seymour S. Kety, "Those who attended this symposium found it to be an extremely worthwhile opportunity for reviewing the broad field of nervous system metabolism in a manner which created a sympathetic understanding of the different disciplines from as wide a spectrum as electron microscopy, biophysics, physiology, biochemistry, and pharmacology".... The international neurochemical symposia were originated in 1954 by Elkes and Richter in England and by Flexner, Folch-Pi, Kety, and Waelsch in the U. S.

Physiological Congress Held in Brussels About 3,500 physiologists convened in Brussels for the XX International Physiological Congress (July 30-Aug. 4). The significance of neurophysiology was delineated by the fact that often four or more sessions on various aspects of the discipline were being conducted simultaneously. There were important symposia on neuronic inhibition and excitation, chaired by Adrian, which included presentations by Fatt, Feldberg, and Fessard; on the initiation of the sensory discharge, with presentations by Gray, Granit, and Paintal; on the structure and function of the brain, chaired by Fessard, which consisted entirely of papers by Russian scientists including Cupalo, Palladine, and Sarkisov; and a symposium on the reticular formation, chaired by Magoun, and including papers by Moruzzi, Dell, and Bovet. On the final day (Aug. 4), there were special sessions devoted to pharmacology, which consisted largely of reviews.

Mayo Foundation Offers Fellowships in EEG Reginald G. Bickford announces that the Mayo Foundation is offering a limited number of one-year fellowships for training in clinical electroencephalography. The program, which is oriented to the basic requirements of the Board of Qualifications of the American EEG Society, will provide training in electronics, instrumentation, neurophysiology, EEG technic and interpretation (two-hour daily instruction periods for the first six months); thereafter opportunity for personal interpretation according to individual competence.... Candidates for

fellowships must be physicians and preference will be given to those applicants who have had clinical experience in neurology or neurosurgery. For further information, write Dr. R. G. Bickford, Mayo Clinic, Rochester, Minn.

* * *

Puerto Rican Conference Reviews Collaborative Studies on Experimental Brain Damage

* * *

At the University of Puerto Rico School of Medicine in San Juan, a three-day conference (Aug. 29-31) brought together distinguished investigators who currently are engaged in research on perinatal influences which may lead to brain damage and impairment of learning. Collaboratively conceived by the University of Puerto Rico and the National Institute of Neurological Diseases and Blindness, the meeting had many official sponsors: United Cerebral Palsy, Association for the Aid of Crippled Children, National Multiple Sclerosis Society, and the National Science Foundation. Also represented were the National Society for Retarded Children (Richard L. Masland) and the Muscular Dystrophy Associations of America (Hans H. Reese).... The specific purpose of the meeting was to review present studies, both animal and human, on the role of neonatal asphyxia and other factors in the causation of brain damage during early life; and to plot a course for future research in this field. The conferees, composed of leading obstetricians, pediatricians, neurologists, neuropathologists, and a distinguished group of experimental scientists, focused their presentations and round-table discussions on the pathophysiologic, biochemical, and clinical aftermaths of neonatal asphyxia and anoxia. The program ended with a talk by Glidden Brooks, medical director of U.C.P., on future research in cerebral palsy and with concluding remarks from the director of NINDB in which the Institute's collaborative Field Investigations program in cerebral palsy were summarized (see May 1955 Newsletter). These sessions filled three half days and were conducted jointly by Carroll A. Pfeiffer, professor of anatomy at the Medical School in San Juan, and William F. Windle, chief of NINDB's Laboratory of Neuroanatomical Sciences.

Official Receptions Given to Conferees

On Wednesday evening (Aug. 29), high officials representing the Puerto Rican Commonwealth, its university and medical school, welcomed the assembly of conferees and guests at an informal dinner on the beach terrace of San Juan's Caribe Hilton Hotel. After a dinner of succulent roasted pigs, short speeches of welcome were made by E. Harold Hinman, dean of the medical school; Hiram Cancio, acting chancellor of the university; and the Honorable Arturo Morales Carrion, Subsecretary of State.... On Thursday evening (Aug. 30), a colorful reception was given for the conferees by Dona Felisa Rincon de Gautier, mayoress of San Juan, who, in 1954, was elected "Woman of the Americas." Held in the picturesque Casa Alcadia, the dinner was followed by a recital of Puerto Rican folklore music interspersed with historic commentaries by Don Rafael, the island's chief of protocol.... The

final reception on Friday evening (Aug. 31) was given in their ocean front villa by Dr. and Mrs. Jose L. Robert, the brother and sister-in-law of Academy member Marisa I. R. Ramirez de Arellano.

Pregnant Monkeys To Be Used as Research Subjects

A more general purpose of the Puerto Rican conference was to consider the use of monkeys as research animals in experimental cerebral palsy and mental retardation and to inaugurate the collaborative research project in this field between NINDB's Laboratory of Neuroanatomical Sciences and the department of anatomy of the medical school in San Juan. The monkeys for this project comprise the natural colony on Santiago Island off the eastern shore of Puerto Rico, the only free range monkey colony in the New World. Accordingly, the last afternoon (Aug. 31) of the conference was devoted to a description of the monkey colony (Jose G. Frontera) and to dissertations on learning and memory in monkeys (Harry F. Harlow) and on their breeding and care (Gertrude van Wagenen). On Saturday morning (Sept. 1), interested conferees were taken on a walkie-talkie tour of the Santiago Island monkey colony.

* * * * * *

Neurosurgical Forums To Be Held in San Francisco

Two surgical forum sessions devoted to reports of research in neurosurgery are to be held at the 42nd Clinical Congress of the American College of Surgeons at the Fairmont Hotel in San Francisco (Oct. 8-12). To be featured in the program are two panel discussions: one on the surgical management of intracranial aneurysms and arteriovenous malformations, the other on the surgical management of other cerebral vascular disorders. Russell Meyers will moderate the panel discussion on aneurysms and arteriovenous malformations, having as collaborators W. B. Hamby, C. F. List, and Francis Murphey. The panel discussion on the surgery of other cerebral vascular disorders will be moderated by E. S. Gurdjian with H. J Svien, E. B. Boldrey, and W. H. Sweet collaborating. In addition, there will be an afternoon session (Oct. 12) of miscellaneous neurosurgical presentations conducted by Howard C. Naffziger of San Francisco.

Penfield To Be Guest Speaker at Neurosurgical Congress

Wilder Penfield will be the principal guest speaker at the Sixth Annual Meeting of the Congress of Neurological Surgeons at the Palmer House in Chicago, November 1-3. He will give two addresses, the first on the function of the temporosylvian fissure and the second an historic sketch, Dawn of Medicine in the Aegean. The program of the congress will center on the ophthalmologic, endocrine, and surgical aspects of the pituitary.... Inquiries should be directed to Dr. Philip D. Gordy, 1007 Delaware Avenue, Wilmington, Delaware.

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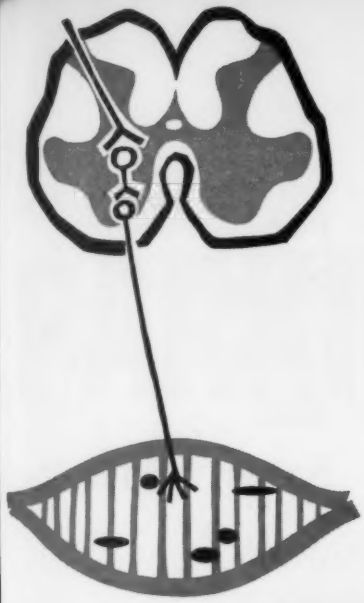

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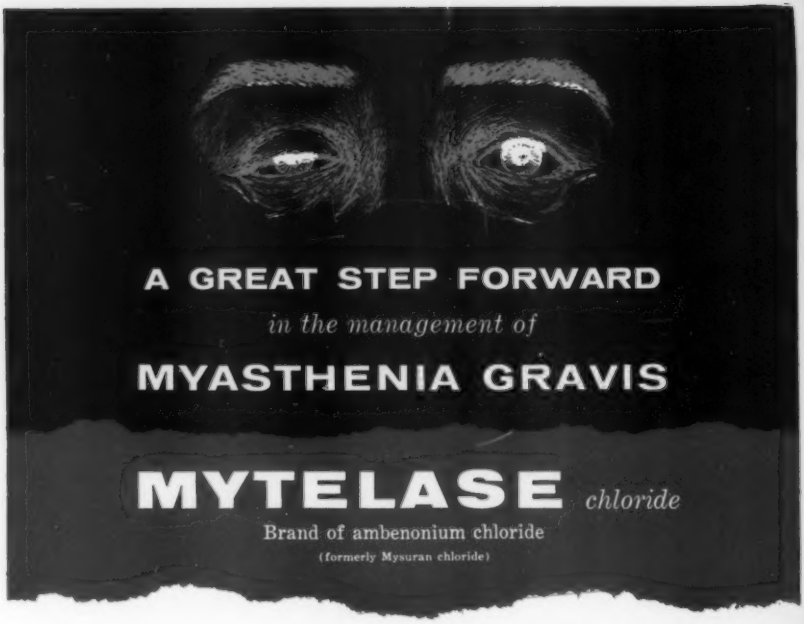

Mytelase chloride (WIN 8077) is a new antimyasthenic compound with definite advantages over older cholinergics.

More pronounced improvement

Patients "... feel better, are stronger, and are closer to their normal health."[1]

More prolonged action

As a rule Mytelase "... has roughly twice the effectiveness per milligram of neostigmine in reducing the symptoms of myasthenia gravis, and approximately twice the duration."[2] Some patients can replace their former 10 to 60 tablets daily with as few as 2 tablets of Mytelase; sleep need not be interrupted for dosage.[1]

Fewer gastro-intestinal side effects

Supplied: Tablets, scored, of 10 mg. and 25 mg., bottles of 100.

Write for booklet discussing in detail clinical experience, dosage, side effects and precautions to be observed.

1. Schwab, R.S.; Marshall, Clare K.; and Timberlake, William: *J.A.M.A.*, 158:625, June 25, 1955.
2. Schwab, R.S.: *Am. Jour. Med.*, 19:734, Nov., 1955.

Mytelase, trademark

Winthrop LABORATORIES NEW YORK 18, N. Y.